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THE FIBRINOLYTIC ACTIVITY OF HUMAN ENDOMETRIUM STUDIED IN TISSUE CULTURE

Part I Normal Endometrial and Decidual Tissue

BY

STIG KULLANDER AND BENGT KÄLLÉN

Introduction

It has long been suggested that fibrinolytic processes play an important role in normal menstruation and in abnormal uterine bleeding It was supposed that enzymes of a fibrinolytic character are formed in the endometrial glands (Whitehouse 1914 Kross 1924) and such enzymes were demonstrated in endometrial extract (Huggins Vail and Davis 1943) Quantitative determinations were made by Page Glendening and Parkinson (1951) Extracts from endometrium were permitted to digest bovine fibrin at 28° C An increased activity in pre menstrual endometrium was demonstrated Caffier (1930) tested the proteolytic effect of human endometrium using Loeffler plates as a substrate Also according to his findings the pre menstrual tissue was rich in proteolytic ferments but he also found such activity in the decidua during the first four months of pregnancy

According to more recent workers (Astrup 1957) the fibrinolytic activity is regarded as due to a complicated system The enzyme itself (plasmin or fibrinolysin) is usually present as a proenzyme (plasminogen or profibrinolysin) and may become transformed by activators some of which are present as tissue activators in various organs According to Albrechtsen (1956 1957) human endometrium contains much activator during the secretory phase in association with abnormal bleeding

lization or clot lysis. The action of LEe is supposed to be that of a competing substrate of plasmin (Müllertz 1957). Röhl (1959) used the same method when culturing the highly fibrinolytic tissue found in human prostatic hyperplasia. A more detailed investigation of the fibrinolytic effect of this tissue in the presence of LEe (Källen and Röhl 1960) indicates that besides the plasmin activating system another group of proteolytic enzymes is present in some cases of prostatic hyperplasia.

In the last mentioned investigation a method of judging the total fibrinolytic activity of a tissue was used resembling that used by Fleischer and Loeb (1915) in their study of tissue fibrinolysins in various organs. After explantation in plasma clot cultures the number of explants with such a degree of clot digestion that the explant becomes loose is determined for each day under various experimental conditions.

Review of Tissue Culture Studies of Human Endometrium

A relatively large number of papers have been published on the subject of keeping alive in tissue culture milieu human endometrium removed at curettage or taken from operation specimens after hysterectomy. In early studies, *e. g.* Caffier (1928), Heim (1928) and Traut (1928) demonstrated the possibility of maintaining endometrial tissue *in vitro* for a short time. Decidual tissue was also cultured but according to Caffier active growth was obtained only from decidua taken before the fourth month of pregnancy. Fibrinolysis was a strong characteristic of endometrial tissue when explanted to plasma clot cultures. Hirsch and Jones (1933) mention that strong fibrinolysis was evident even within the first 24 hours.

Randall, Stuermer and Stein (1950 a) investigated the role of oxygen tension, temperature and pH of the culture fluids on organ cultures of endometrium in a liquid medium. Differences were described between endometrium taken during the proliferative phase and that taken during the secretory phase.

Marcuse (1955) distinguished between polygonal cells which he interpreted as epithelial and spindle shaped cells interpreted as fibroblasts or stroma cells. Moore (1956) mainly

during the proliferative phase and when the endometrium is hyperplastic (MHC). It is completely lacking in normal decidua. The determination of the amount of activator present was made by Albrechtsen from extracts which were incubated with bovine fibrin plates. Heating these plates to 85° C destroys their plasminogen content and the resulting plates can only react with plasmin (fibrinolysin) in an already activated state. This fact makes it possible to differentiate between the content of plasmin and plasmin activator in an extract. Albrechtsen was not able to demonstrate the presence of plasmin in the endometrium. Earlier determinations of the fibrinolytic enzyme of the endometrium (Huggins *et al.* 1943, Page *et al.* 1951 and others) employed substrate which also contained plasminogen and were therefore unable to demonstrate the presence or absence of already activated plasmin.

In the present study the fibrinolytic activity of normal human endometrium cultured in plasma clot tissue culture has been investigated. In a further report, similar studies on abnormal and malignant uterine tissue will be presented.

Fibrinolytic Phenomena in Tissue Culture

Since the early days of tissue culture in plasma clots it has been observed that many tissues have considerable ability to digest the clot, thereby destroying the framework along which cells grow. It has also been noted that different tissues show a varying capacity for clot digestion.

Early efforts to overcome this lytic activity consisted of the addition of sodium linoleate (Traut 1928) or soya bean extract (Fischer 1949), or the continual breaking down of plasma was compensated for by the addition of new substrate at regular intervals. According to Fischer (1946), Fawcett (1955) and Cobb, Kiefer and Wood (1955) the proteolytic activity is due to an activation of plasminogen in the clot by activators produced by the explanted tissue. Ingemanson (1959) succeeded in delaying this process by adding lysin ethyl ester (LLe) to the clots in concentrations of 2.5 to 10 mg/ml and in this way obtained good outgrowth of rat endometrial cells without vacuo-

The curettage was performed for such reasons as sterility erosion or polypus of the cervix etc Histological controls of the endometrial specimens were made They were subdivided into the following groups using histological criteria as a basis (1) proliferative phase (2) phase intermediate between proliferative and secretory phase with cells showing signs of basal secretion and (3) secretory phase In some cases curettage was made during menstrual bleeding Endometrial tissue in senile involution was obtained by curettage from post menopausal patients who were to be operated upon for prolapse

The tissue specimens removed at operation were placed in sterile Tyrode s solution and were cultured within an hour

Cultures were prepared in Carell flasks (D 5 cm) in a plasma clot consisting of 50 per cent unheparinized cockerel plasma (from animals about 1 year old) and 50 per cent chick embryo extract (from embryos age 8—10 days) Two groups were studied one a *control group* and one a *LEe group* where lysine ethyl ester was added to a final concentration of 2 5 mg/ml Next day a supernatant consisting of human serum from healthy adult blood donors was added In each flask 1 ml of solid phase and 1 ml of fluid phase was present As a rule 27 cultures were made in each group from each tissue specimen

The cellular outgrowth was observed with the aid of phase contrast microscopy The fibrinolytic process was registered by the method of Kallen and Rohl (1960) which consists of counting the number of explants showing a complete digestion of surrounding plasma and thus becoming loose This number was determined daily The cultures were followed for up to 14 days without change of the fluid phase The time necessary for half of the explants to become loose was determined for each experimental group and will be called LT_{0}

Results

Cellular Outgrowth from the Explants

Little can be added to the descriptions already published in the literature on the subject A good growth made up of both fibro

obtained growth of stroma cells, but also described epithelial cells which were ciliated. Similarly, Papanicolaou and Maddi (1958, 1959) have described outgrowth of epithelial cells from different stages of the endometrical cycle and various types of phagocytes, derived from stromal and epithelial cells. On the other hand Hellweg and Shaka (1959) consider the whole of the outgrowth zone to be made up of stroma cells, the growth changes of the epithelium being shown only in a covering of the raw surfaces of the explant. They further demonstrated the presence of granulocytes in the cultures, partly derived from the explants and partly formed from migrated stroma cells.

In the cultures prepared by Hellweg and Shaka, no umbilical cord serum was present. This might explain the lack of epithelioid growth if the results of Randall *et al.* (1950 b) and Kiszely (1953) are accepted. The former authors showed that in a synthetic medium only fibroblastic growth was obtained from endometrium but in a medium containing umbilical cord serum epithelioid growth was also seen. Kiszely described epithelioid growth from decidua but from other endometrial tissue it occurred only in the presence of umbilical cord serum.

Different vigour of growth has been ascribed to different stages of endometrial tissue. Hellweg and Shaka (1959) obtained the best outgrowth from mid-proliferative mucosa and from that taken about day 22 in the menstrual cycle. Moore (1956), on the other hand, obtained equally good growth in all normal endometria but a better growth in tissue taken from carcinoma and endometrial hyperplasia. Figge (1960) studied the morphology and biochemistry of endometrial cells cultured from various stages of the menstrual cycle. According to his results the epithelioid cells seen in the outgrowth are derived from the surface and the glandular elements. This author thinks that endometrium in culture fails to maintain the physiologic potentials of the antecedent tissue.

Material and Methods

Endometrial tissue was obtained at curettage and decidual tissue from Caesarean sections or therapeutic abortions. Tissue was taken only from women without known bleeding abnormalities



F g 2 Phase contrast m c ophotograph of cells grow n g out f om a prol fera t e endometr um taken 3 days after explantat on. Note small ep theloid cells × 200

gro th had commenced These facts ind cate that there is fibrino l t c act ity n both the outgro ing cells — result ng in the d ntegration of the cell sheets ment oned abo e — and n the t ssue rema n ng in the primary explant Among the outgro ing ells the ep thel o d sheets appeared to have the strongest fibr no- l t c propert e

The Rate of Fibr olysis in the C lt res

F g 5 illustrates the method of registrat on used Here the number of explants st ll attached after var ous t mes of ncul a t on s plotted for some characterist c cases In Case A a very rap d f br noly s took place Half of the explants became loose



Fig. 1. Phase-contrast microphotograph of cells growing out from a secretory endometrium taken 2 days after explantation. × 150.

blastic, stromal cells and epithelioid cells, was seen in endometria from both proliferative and secretory phases. Strong epithelioid outgrowth was seen also in cultures of decidua from both term and 3rd to 4th months gestations. In cases of senile endometria the fibroblastic outgrowth dominated but epithelioid cells were sometimes seen. In Figs. 1—4 examples of cellular outgrowth pattern are shown from various stages of uterine mucosa.

In the cellular sheets developing from the explants a rapid disintegration could often be seen, starting with vacuoles and resulting in a complete break down of the sheets and a loosening of the original explants. In many cases, however, cells could continue to live in the clot after the loosening of the original explant. On the other hand the explant could come loose before cellular out



Fig. 4. Phase contrast microphotograph of cells growing out from a senile endometrium taken 5 days after explantation. × 200

plasma clot. Only the means of the explants prepared from one tissue specimen are therefore used and each is regarded as one observation. The LT_{50} time may be regarded as such a mean value. Comparisons between different tissues will be based on a number of different tissue specimens.

LT_{50} Values of Different Endometrial Types and Deciduæ

(1) *Secretory phase.* Twelve biopsies were taken from endometrial tissue which according to the histological diagnosis was in a typical secretory phase. The LT_{50} in control cultures — without LEe — varied between 2.5 and 4.5 days. The mean was 3.4 ± ± 0.23.

If cultures containing LEe are compared with control cultures a lengthening of the LT_{50} is seen amounting to between $^3/_4$ to 6



Fig. 5. Phase-contrast microphotograph of cells grown out from a decidua (3rd month) taken 11 days after explantation. Note epithelial sheet. × [illegible]

between the 2nd and 3rd days of incubation. The LT_{50} time is therefore 2.5 days. In Case B there was a lower rate of fibrinolysis resulting in a LT_{50} time of 11.5 days. In Case C some fibrinolysis occurred but the LT_{50} value was not reached during the 14 days of observation. In this case LT_{50} is > 14. In Case D finally no fibrinolysis was observed during the 14 days of observation. Here LT_{50} is said to be $= \infty$.

It can be seen especially in the cases of low fibrinolysis (Case B and C) that the range of fibrinolytic capacity of the different explants is wide resulting in a gradually falling curve. Many factors may influence the activity of the individual explant: its size, the proportion of stroma and epithelium it contains, the degree of trauma at the culturing and its position within the

regular menstrual cycles The LT_{50} in control cultures varied between 2 5 and 14 days with a mean of 4 44 ± 1 38 This mean is not significantly different from that of the secretory phase cultures (t = 1 77 at 16 d f P ≈ 0 1)

The lengthening of LT_{50} obtained by addition of LEe varied considerably in different tissue specimens In 6 of the 8 cases the lengthening was more than 7 days i e in these 6 cases fibrinolysis occurred more slowly in LLe cultures than it did in the secretory phases In the other 2 cases a lengthening of only 3 and 3 5 days was obtained which falls within the limits of the secretory phase There was no correlation between age of the tissue donor and length of retardation of fibrinolysis with LLe nor could any findings in the histology be correlated with this In one case no fibrinolysis whatever took place in the presence of LEe and in 4 cases the LT_{50} value was not reached at 14 days

(3) *Intermediate secretory-proliferative phase* In 8 cases the histological examination showed tissue in a stage intermediate between the proliferative and secretory phase The LT_{50} in control cultures was 3 69 ± 0 85 varying between 1 5 to 7 5 days The lengthening of LT_{50} obtained after addition of LLe varied considerably In 5 cases the retardation was less than 7 0 days and is thus not significantly different from that of secretory phases In the other 3 cases the retardation was more than 7 0 days in 2 cases LT_{50} had not been reached at 14 days in the LEe cultures in one case no signs of fibrinolysis were present in LFe cultures

(4) *Senile endometrium* In 8 cases endometrium from post menopausal women was cultured In 2 cases no fibrinolysis took place either in control or in LFe cultures In 2 cases the LT_{50} in control cultures was more than 14 days in LEe cultures no fibrinolysis took place In 2 cases LT_{50} was 11 5 days in control cultures and in one case only 6 days In the latter case and in one of the former LT_{50} was not reached with LLe during 14 days and in the other of the former cases no fibrinolysis took place with LLe

(5) *Decidual tissue* Fourteen specimens of decidual tissue have been studied 9 of these were taken from *pregnancies* of from 3 to 5 months of gestation and 5 were taken during Cæsarean sections at term In 2 cases of the former group a certain amount of

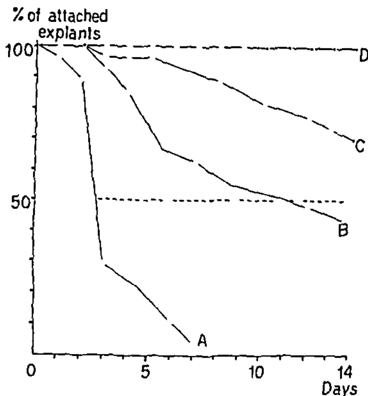


Fig. 5. Diagram illustrating different fibrinolytic activity. The percentage of *attached explants are plotted against age of cultures. A strong fibrinolysis* (secretory phase). B moderate fibrinolysis (senile endometrium). C faint fibrinolysis (senile endometrium). $LT_{50} > 14$ days. D no fibrinolysis (decidua 3rd month).

days. The mean lengthening of LT_{50} caused by LLe is 2.3 ± 0.46 days (standard deviation 1.53 days). At a P value of 0.01 fiducial limits will be 0 and 7.04 days.

Of these 12 biopsies, 5 were taken from women over 40 years. No difference in activity was seen between these and the others.

In another 2 cases the biopsy was taken during menstrual bleeding. In one case LT_{50} was 3.5 and *the lengthening caused by LLe* was 5.0 days; in the other, LT_{50} in controls was 3.0 and the *lengthening* by LLe 3.5 days.

(2) *Proliferative phase*. Eight biopsies were taken from endometrial tissues which, according to the histological diagnosis, were in a typical proliferative phase and were taken from women with

rate retardation seen in secretory endometria was obtained The former response appears to be more typical of the proliferative phase for the following reasons When an endometrial biopsy shows a proliferative phase it cannot with certainty be said that a secretory phase will follow i e that a normal cycle is present If however endometria showing proliferation with signs of commencing secretion are obtained by biopsy it suggests that a normal cycle is present In the group of such intermediate endometria studied here behaviour similar to secretory endometria is seen and also that resembling the larger group of proliferative endometria In one case especially where only in a few places were signs of commencing secretion seen in the sections the biopsy behaved as a typical proliferative endometrium with a slow fibrinolysis in the presence of LEe This fact together with the higher frequency of specimens showing slow fibrinolysis with LEe supports the opinion that slow fibrinolysis is typical of proliferative endometrium

What then is the basis of the different behaviour of the different endometrial phases in the presence of LEe? Fibrinolysis in the presence of LEe indicates either a very strong production of plasmin which first breaks down all LEe and then digests the network *or* the presence of other proteolytic substances not arrested by LEe If the former explanation is correct stronger fibrinolysis could be expected in control cultures made with endometrium from the secretory phase than from the proliferative phase A slight difference of this nature was present but it was not statistically significant thus favouring the second opinion

If this latter opinion is correct it would mean that a higher activity of non specific proteolytic enzymes — not activators of plasmin — would be present in the secretory phase than in the proliferative phase In our series there are no indications of a higher activator content in the secretory stage Albrechtsen (1956) on the other hand demonstrated a higher content of activator substance in the secretory phases

Using the same methods as described in the present paper the influence of hormones on the production of proteolytic enzymes and plasmin activators can be studied Such studies have been made by the present authors and will be presented separately

fibrinolysis occurred in control cultures. In one of these cases, LT_{50} was reached at 8 days, in the other it was not reached at 14 days. In all other cases no fibrinolysis whatever could be seen in either control, or LEe cultures.

Discussion

From the findings presented above it is apparent that different types of endometrium behave differently in tissue culture with respect to their ability to digest the plasma clot. In post menopausal mucosa, very low fibrinolytic activity was found. This agrees with Albrechtsen's (1956) findings. Similarly, we have found little or no fibrinolytic activity in decidual tissue. In only 2 cases out of 14 were signs of fibrinolysis found. Albrechtsen also found a faint activator content in 2 out of 35 cases of artificially interrupted pregnancies of 4 to 16 weeks duration.

Endometrial tissue obtained from women with apparently normal menstrual cycles behaved differently in tissue culture. A marked fibrinolytic effect could be seen. Albrechtsen (1956) found a lesser amount of plasmin activator in secretory endometria from women over 40 years and with menstrual cycles. He thought this phenomenon would be correlated to reduction of menstruation with increasing age. In our series no difference was found between endometria in the secretory phase, taken from women under or over 40 years.

There was no significant difference in rate of fibrinolysis in control cultures made from secretory and proliferative endometria. In cultures prepared with LEe however there was a difference. In secretory endometria LEe addition resulted in a moderate reduction of the fibrinolysis. This might be due partly to the competitive action between LEe and plasmin and partly to the cell toxic effect obtained by LEe (Ingemansson 1959). The latter effect is especially pronounced on the fibroblastic growth but also results in a lengthening of the lag time of the epithelial growth.

With proliferative tissues the addition of LEe to the cultures resulted in most cases in a pronounced retardation of the fibrinolytic activity which is significantly different from that seen with secretory endometrium. In some cases however only the mode

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SUMMARY

The fibrinolytic activity of normal human endometrial and decidual tissue kept in plasma clot tissue culture has been studied. The following observations were made.

Senile endometrium and decidual tissue from the 3rd to 5th month of gestation and from full term pregnancies showed little or no fibrinolytic activity *in vitro*.

Endometrium from women with normal menstrual cycles showed a strong fibrinolytic activity. In control cultures it was the same in secretory and proliferative phases. After addition of EAC to the cultures a moderate retardation was obtained of the fibrinolytic activity of secretory phase cultures but a significantly more marked retardation in proliferative phase cultures. It is suggested that this is due to a higher content of non-specific proteolytic enzymes (not plasmin-related) in the former phase.

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however, they are most frequently within normal ranges According to them the decisive factor is the mutual relationship of the fractions of the 17 ketosteroids especially the relation between the androgenous steroids secreted by the ovaries and the adrenal cortex In healthy women this ratio between androsterone and etiocholanolone is 0 97 and the androgenous quantity secreted by the ovaries is smaller than the quantity secreted by the adrenal cortex In Stein Leventhal patients the ratio is frequently inverted Recently a theory has also been advanced according to which there is a congenital ovarian malformation which is the consequence of an excessive chorionic gonadotrophic stimulation of the gonads of the fœtus during embryonal development The German gynæcologist Stange (1959) bases this theory on many animal experiments By chorionic gonadotrophic treatment of long duration he caused similar changes to arise in the gonads of the mouse as occur in Stein Leventhal patients

Although the ætiology is not clear and possibly is dependent on a complicated hormonal process the treatment of the syndrome has been simple Ovarian wedge resection was initially the sole treatment employed Attempts have also been made at several hormonal therapies but lasting results have not been obtained by them In wedge resection a large portion of the ovarian cortex is removed whereafter the symptoms in general disappear with the exception of the hirsutism which generally remains unaffected by the treatment

In 1958 Allen and Woolf reported on a series including 22 patients who were treated with resection of the medullary portion of the ovaries They also put forward a new theory of the ætiology According to it remnants of the testicular portion of the still indifferent gonads are present in the medullary portion of the ovary This normally becomes rudimentary in women while the ovarian cortex is developing around it According to the authors mentioned above these remnants secrete so much androgenous hormones that they hinder the action of the pituitary which again brings about ovarian dysfunction and symptoms present in the syndrome They based this assumption on macroscopic and microscopic studies of the ovaries In macroscopy the ovaries are two to five times larger than normally light grey and compact with a

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MEDULLARY RESECTION OF THE OVARIES IN TREATMENT OF THE STEIN-LEVENTHAL SYNDROME

Report of 11 Cases

BY

HANNA KALLIO

In 1935 Stein and Leventhal first described the syndrome which since then has been known under their name They reported on seven patients with common traits of oligomenorrhœa or amenorrhœa as well as enlarged ovaries and sterility Hirsutism and a tendency to obesity also occurred They considered the amenorrhœa and the ovarian changes to be caused by the hormonal secretion of the anterior pituitary After wedge resection of the ovaries the symptoms disappeared

Ever since then the syndrome has been the subject of study and numerous theories about its ætiology have been put forward Some investigators consider the thickened tunica albuginea a mechanical hindrance to ovulation Delson (1949) has suggested that a circulatory disturbance occurs in the ovary caused by straightening of the arteriolar spirals and rise in blood pressure in them The theory according to which the symptoms are a result of the disturbed balance in the hormonal secretion from the anterior pituitary the adrenal cortex and the ovaries has received great support According to an investigation published in 1959 by Pesonen Timonen and Mikkonen the total amounts of gonadotrophic hormones œstrogens and 17 ketosteroids vary

The Series

The series comprises 11 women aged between 20 and 40 years all of which displayed features characteristic of the Stein Leventhal syndrome The case histories and the pre-operative findings are compiled in Table I The age of menarche varied between 12 and 16 years Axillary and pubic hair appeared at the normal age as did the breasts develop All patients had oligomenorrhœa or secondary amenorrhœa In some of the patients menses were regular to begin with but in others were irregular from the menarche The periods of amenorrhœa varied greatly from two to five months up to two years None of these patients had metrorrhagic bleeding Eight patients were married and all were sterile though in two this was secondary One hade given birth to a healthy child five years ago and the other three years ago Hirsutism also occurred in eight patients but it varied considerably in degree Some of them had only a slight facial hairy coat and pubic hair of virile type whereas in others the breasts the thighs and even the legs were covered by a thick hairy coat Hirsutism had been present in some for many years while in others only a short time Obesity was characteristic of 4 patients only Four patients also complained of pain in the lower back and

Table I *Case History and Pre-operative Observations*

No.	Age Yrs	Age of Menarche Yrs	Duration of Amenorrhœa	Duration of Symptoms Yrs	Hirsutism	Obesity	Sterility	Pain	Enlarged Ovaries
1	8	13	3—6 mths	15	—	—	+	—	—
	30	1[illegible]	2 mths—[illegible] yrs	10	+	+	+	—	+
3	29	14	4—5 mths	14	+	+	+		+
4	40	14	2—3 mths	20	—	—	—	+	+
5	[illegible]7	13	3—6 mths	14	+	+	+	—	+
6	30	14	—14 mths	14	—	+	+	—	+
7	21	13	3—6 mths	5	+	—	—	+	+
8	20	1[illegible]	1— mths	2	+	—	—	—	+
9	34	13	1—3 mths	20	+	—	+	+	—
10	21	15	2—3 mths	3	+	—	+		+
11		16	—7 mths	6	—	—	+	+	—

smooth surface. When they are split, a thick albuginea can be seen in them, under which there are visible, fairly small ovular follicles containing a brownish fluid, which frequently appear in lines. A thickened luteinized thecal cell layer forms the wall of the follicles. An abundance of blood vessels run through the tunica albuginea in the same way as through the cortex of the testis. The largest portion of the enlarged ovary is, however, made up by the medulla, in which hyperplasia of the stromal cells is discernible in microscopy. Luteinization is seen as well as hilar cells containing fatty substances. Similar changes to the ones reported by these investigators have also been described by the French workers Laffarque, Gares, Luscan and Portier (1957) in their study on the Stein Leventhal syndrome. According to them in the ovaries there is a stroma with an ample connective tissue and polyhedral thecal cells occurring in patches. Primary follicles are scanty in the ovarian cortex and most of them do not get detached or luteinized but undergo involution to connective tissue.

Allen and Woolf (1959) in operating removed this hyperplastic medullary portion with utmost care, destroying as little as possible of the ovarian cortex, the insufficiency of which they considered obvious. The post-operative observation period was one to six years. The results were extremely favourable. In all patients the menses became fairly regular. None needed hormonal therapy. In regard to sterility the results were also fairly good. Twelve of the patients were married and wanted children; two of them had given birth to a normal child, two had miscarried and one had a premature birth. The operation had a very slight effect on the virilism. In those who had an enlarged clitoris it was found to diminish in size, but hirsutism definitely decreased only in one, while in some others there was a slight diminution of the hair growth.

The following is a presentation of some patients with the Stein Leventhal syndrome who were admitted to the Women's Clinic I of the University of Helsinki during the years of 1957 to 1959 and who were treated with medullary resection.

The Series

The series comprises 11 women aged between 20 and 40 years all of which displayed features characteristic of the Stein Leventhal syndrome. The case histories and the pre-operative findings are compiled in Table I. The age of menarche varied between 12 and 16 years. Axillary and pubic hair appeared at the normal age as did the breasts develop. All patients had oligomenorrhœa or secondary amenorrhœa. In some of the patients menses were regular to begin with but in others were irregular from the menarche. The periods of amenorrhœa varied greatly from two to five months up to two years. None of these patients had metrorrhagic bleeding. Eight patients were married and all were sterile though in two this was secondary. One hade given birth to a healthy child five years ago and the other three years ago. Hirsutism also occurred in eight patients but it varied considerably in degree. Some of them had only a slight facial hairy coat and pubic hair of virile type whereas in others the breasts, the thighs and even the legs were covered by a thick hairy coat. Hirsutism had been present in some for many years while in others only a short time. Obesity was characteristic of 4 patients only. Four patients also complained of pain in the lower back and

Table I *Case History and Pre-operative Observations*

No	Age Yrs	Age of Menarche Yrs	Duration of Amenorrhœa	Duration of Symptoms Yrs	Hirsutism	Obesity	Sterility	Pain	Enlarged Ovaries
1	[illegible]8	13	3 6 mths	15		–	+		–
2	30	15	mths–2 yrs	10		+	+		+
3	[illegible]9	14	4–5 mths	14	+	+	+		+
4	40	14	– 3 mths	20	–	–	–	+	+
5	[illegible]	13	3–6 mths	14	+	+	+	–	+
6	30	14	2 12 mths	14		+	+	–	+
	21	13	3–6 mths	8	+	–	–	+	+
8	[illegible]	1	1–2 mths	[illegible]	+		–		+
9	34	13	1–3 mths	20	+	–	+	+	–
10	[illegible]	15	2–5 mths	3	+	–	+		+
11		16	5–7 mths	6	+	–	+	+	–

the pit of the stomach The clitoris was somewhat enlarged in only one It was established by bimanual examination that in 10 patients the ovaries were enlarged the size varying between that of a plum and a hen s egg

Hormonal analysis was carried out on 10 patients (Table II) The gonadotrophins œstrogens and 17 ketosteroids were examined The gonadotrophins (I SH) varied In 4 cases they were normal in 5 above normal and in 1 below normal The œstrogen were low in all The values of 17 ketosteroid varied from 6 0 to 18 4 mg a day the normal being 6 to 10 mg a day In five the value exceeded normal limit though in one only was it considerably increased in half the patients the value was within normal range

In 5 patients fractioning of 17 keto teroids was performed and in 3 of them the ratio androsterone etiocholanolone was above one whereas it was below in two (Table III)

On the basis of case historie bimanual examination and hormone analysis the diagnosis of Stein Leventhal syndrome was made and operation was decided upon An attempt had been made

Table II *Hormonal Analyses*

No.	Gonadotrophins M U a Day	Œstrogens I U a Day	17 ketosteroids mg a Day
1			
2	>10 <40	50	18 4
3	>10 <40	50	13 8
4	>10 <40	5	11 1
5	>40	100	9 6
6	>40	150	6 9
7	>10 <40	500	13 3
8	>20 <80	50	6 0
9	<10	75	8 1
10	>40	50	9 6
11	>40	200	13 3

Table III 17 *ketosteroid Fractions*

No	U		DHA		A		E		Rest		A E
	mg	%	mg		mg		mg	%	mg		
3	08	5.9	14	98	37	267	66	480	13	96	051
5	08	83	12	125	3.6	379	33	344	07	73	11
7	07	53	2.2	165	48	361	47	357	09	08	10
9	03	37	08	99	39	481	22	272	09	111	18
11	01	6.8	24	181	37	278	4	405	09	68	07

U fraction containing hydrolysis artefacts of the DHA fraction and meta bolites of unknown origin DHA dehydro-epi androsterone A androsterone E etiocholanolone Rest 11-oxygenated 17 ketosteroids

at hormone therapy with every one of the patients in some for many years but entirely without success Many of them had bleeding only once after the hormone injection which had to be repeated regularly to produce further bleeding

The Method of Operation

Instead of the usual wedge resection the procedure wa as fol lows The ovary was split along its longitudinal axis and the ovarian cortex was left intact while the medullary portion was removed as carefully as possible The size of the removed portion varied considerably from 2 to 3 g up to 30 to 40 g dependent on the size of the ovaries After removal of the medullary portion the wound was closed with buttonhole stitches in two layers after which the ovaries were usually practically normal in size

Histological Results

Histological examination was made on ovarian tissue removed at operation in ca es with features characteristic of the Stein Leventhal syndrome (Table IV) In nine samples enlarged follicles could be seen at the border between the cortex and the medullary layer the wall of which was formed by a thickened thecal cell layer The thecal cells were luteinized in most of the samples (Fig 1) In samples where there was also ovarian cortex a

the pit of the stomach. The clitoris was somewhat enlarged in only one. It was established by bimanual examination that in 10 patients the ovaries were enlarged, the size varying between that of a plum and a hen's egg.

Hormonal analysis was carried out on 10 patients (Table II). The gonadotrophins, œstrogens and 17-ketosteroids were examined. The gonadotrophins (FSH) varied. In 4 cases they were normal, in 5 above normal, and in 1 below normal. The œstrogens were low in all. The values of 17-ketosteroids varied *from 6.0 to 18.4 mg. a day*, *the normal being* 6 to 10 mg. a day. In five the value exceeded *normal limit*, though in one only was it considerably increased; in half the patients the value was within normal range.

In 5 patients fractioning of 17-ketosteroids was performed, and in 3 of them the ratio androsterone : etiocholanolone was above one, whereas it was below in two (Table III).

On the basis of case histories, bimanual examination and hormone analysis the diagnosis of Stein-Leventhal syndrome was made, and operation was decided upon. An attempt had been made

Table II. *Hormonal Analyses*

No.	Gonadotrophins M. U. a Day	Œstrogens I. U. a Day	17-ketosteroids mg. a Day
1			
2	>10 <40	50	18.4
3	>10 <40	50	13.8
4	>10 <40	75	11.1
5	>40	100	9.6
6	>40	150	6.9
7	>10 <40	500	13.[illegible]
8	>20 <80	50	6.0
9	<10	75	8.1
10	>40	50	9.6
11	>40	200	13.3



Fig 2 Hypertrophied medullary portion in which there are light patches of stromal cells differentiated in the direction of thecal cells

thickened tunica albuginea was observed and primary follicles were scanty In eight samples large luteinized stromal cells differentiated in the direction of thecal cells and with plentiful cytoplasm could be seen (Fig 2) In one sample only there was a corpus luteum but obviously this was very old

Results of Treatment

These patients were operated upon fairly recently and it is thus too early to draw definite conclusions However the results up to the present are very promising (Table V) Pre-operatively menses in all patients were extremely irregular periods of amenorrhœa as long as two years occurred Post operatively

Table IV *Histological Results*

No	Below the Thickened Tunica Albuginea Small Follicles in Lines	Thickened Luteinized Thecal Cell Tissue	Luteinized Stromal Cell	Corpus Luteum
1				
	+		+	
3	+	+		
4	+	+	−	
5	+	+	+	
6	+	+	−	
7	+	+	+	−
8	+	+	−	
9				
10	+	+	−	
11	+	+	+	

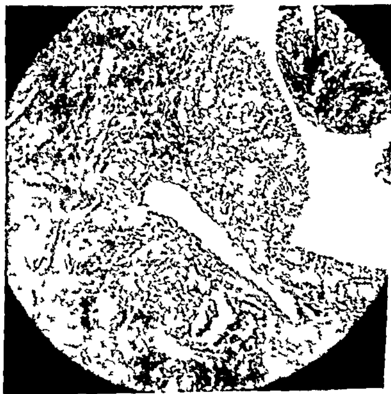


Fig. 1 In the wall of the follicle there is a thickened luteinized layer of thecal cells

syndrome however there seems to be an insufficiency of the ovarian cortex and for this reason it is advisable that the cortex be spared at operation The medullary portion on the other hand, is usually hypertrophied and possibly secretes androgenous steroids Removal of the medullary portion thus would be more in accordance with the ætiology and it might be anticipated to produce better results than removal of the cortex

SUMMARY

Eleven patients treated at the Women s Clinic I of the University of Helsinki were studied The patients ages varied from 20 to 40 years All displayed features characteristic of the Stein Leventhal syndrome. Hormonal analysis was made on 10 patients At operation the medullary portion of the ovaries was removed At histological examination all showed changes of the same nature Post operatively menses became regular in every one of the patients Eight of the patients were married and out of them 5 have become pregnant since the operation

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menses have been regular in all, recurring once a month without any hormonal therapy Eight of the patients were married and all had been sterile three years at least After the operation 2 have given birth to a normal child, 2 are pregnant for the time being, and 1 has miscarried Hirsutism occurred in 8 patients but it decreased in only 2

Table V *Results of Treatment*

No	Year of Operation	Duration of Pre-operative Period	Duration of Post-operative Period	Effect on Sterility	Effect on Hirsutism
1	1957	3—6 mths	28 days	Birth in 1959	
2	1957	2 mths—2 yrs	30—60 days	Abortion in 1959	No effect
3	1958	4—5 mths	28 days	Birth in 1959	Decreased
4	1958	2—3 mths	28—31 days	Unmarried	
5	1959	3—6 mths	28 days	Pregnant	No effect
6	1959	2—12 mths	28—31 days	No effect	
7	1959	3—6 mths	28—30 days	Unmarried	Decreased
8	1959	1—2 mths	30 days	Unmarried	No effect
9	1959	1—3 mths	30 days	Pregnant	No effect
10	1959	2—5 mths	28 days	No effect	No effect
11	1959	5—7 mths	28 days	No effect	No effect

Discussion

Wedge resection used to be the only method of operation employed in the treatment of the Stein-Leventhal syndrome It has been described in numerous publications (Leventhal and Cohen 1951 Buxton and Wiele 1954 Shippel 1955 and others), and the results attained were good at least initially Sometimes cases have occurred in which the condition has recurred after the lapse of a year In the statistics of Allen and Woolf (1959) there is not a single case of recurrence but the period of control is short and the number of patients comparatively small Due to these circumstances it is still too early to make a comparison between the results attained in treatment with wedge and medullary resection In the Stein Leventhal

syndrome however there seems to be an insufficiency of the ovarian cortex and for this reason it is advisable that the cortex be spared at operation The medullary portion on the other hand is usually hypertrophied and possibly secretes androgenous steroids Removal of the medullary portion thus would be more in accordance with the ætiology and it might be anticipated to produce better results than removal of the cortex

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VIRILIZING, MALIGNANT ADRENAL REST TUMOUR OF THE OVARY

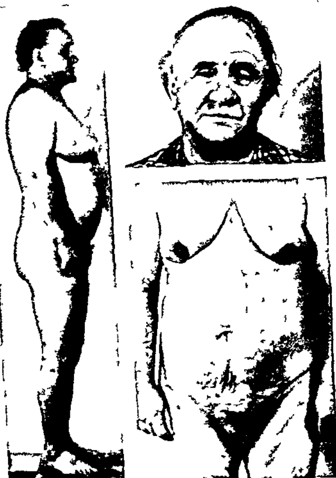
Value of the Corticosteroid Suppression Test in the Diagnosis

BY

LARS BJERSING BENGT SKANSE AND SUNE GENELL

The first case of virilizing adrenal rest tumour of the ovary was described by Bovin in 1908 Since then the histogenesis of the tumour has been the subject of much debate It is widely believed that the tumour originates from ectopic adrenal tissue This view has, however, been criticized chiefly by Teilum (1958), who claims that practically all virilizing lipoid cell tumours of the ovary are variants of arrhenoblastoma (androblastoma diffusum) Some virilizing tumours however cannot be differentiated from one another on histological grounds only and then hormonal studies may be of decisive help

A search of the literature revealed some 35 cases but only 3 established cases with metastases none with hormonal studies (Rottino and McGrath 1939 Burket and Abell 1944 Patil 1951) and no more than 4 in which autopsy had been done (Bauer 1939 Michaelsson 1950 Patil 1951 Bauer and Karl 1952) This paper is concerned with a case of virilizing malignant adrenal rest tumour of the ovary in which the hormone pattern was followed for several periods of the disease and in which complete autopsy was done Certain aspects of this patient s disease were previously discussed by Genell (1951)



F g 1 I at ent s appearance on adm ss n

Report of Case

The p t ent a mult parous woman aged 2 was first seen at the age of 63 becn e f a n a cul n z ng syndrome

Menarche had occurred at the age of 14 after wh ch menstruat on had been reg lar nt l the menopause at 39 She had had 4 uncompl cated preg nancies

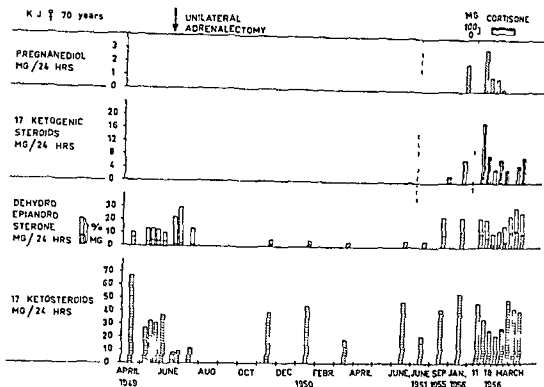


Fig 2 The urinary excretion of 17 ketosteroids dehydroepiandrosterone 17 ketogenic steroids and pregnanediol

In 1942 when the patient was 56 years old she noticed loss of scalp hair with progressing baldness of the male type accompanied by increasing growth of hair on the face and extremities and deepening of the voice She also noticed that the hands and feet had become somewhat larger but no increased prominence of the chin or nose She complained of frequent headaches There was no double vision

Physical examination on admission in 1949 revealed a healthy looking somewhat obese female (weight 79 8 kg height 166 cm Fig 1) The hair on the head was thin and fine with deep recession of the temporal hair line The hair on the face trunk and extremities was coarse The pubic hair was of female distribution The breasts were of ordinary feminine appearance The musculature and the distribution of subcutaneous fat over the body were of masculine type The heart was not enlarged and the blood pressure was 190/100 mm Hg Gynecological examination revealed a normal clitoris and thin atrophic mucous membranes but no tumour

Laboratory studies Roentgenograms of the sella turcica and the skeleton showed no abnormalities except vertebral spondylosis There was no hyper

ostosis frontalis interna. X-ray examination including chest X-ray, plain films of the abdomen, intravenous urography and retroperitoneal pneumography failed to reveal any signs of a pathological condition. An electrocardiogram was normal. Hb 160 g per 100 ml, RBC 4.6 mill per cu mm, WBC 9,300 per cu mm with a normal differential count. Routine analysis of the urine was normal. A glucose tolerance test gave a normal blood sugar curve. The B M R was +38 and +26 per cent. The serum electrolytes lay within normal limits. The urinary excretion of 17-ketosteroid (17-KS) fluctuated between 31 and 68 mg/24 hours as determined by the method of Jensen and Totterman (1952 a). The excretion of dehydroepiandrosterone (DHEA) as determined by the method of Jensen and Totterman (1952b) varied between 3.6 and 7.0 mg/24 hours (see also Fig 2). The urinary excretion of gonadotrophic substances was 65 M U and of œstrogens 30 M U per 24 hours.

On June 16, 1949, the adrenals were explored by the retroperitoneal approach. The right adrenal which appeared enlarged but free of tumours was removed. At operation a biopsy specimen was taken from the left adrenal. Histological examination revealed the presence of nodular hyperplasia of both adrenals.

The post-operative course was uneventful, but the masculinizing syndrome showed no tendency to subside. Initially the urinary excretion of 17-ketosteroids fell but rose again to the pre-operative level within 5 months (Fig 2).

The patient's disease was rather stationary but on April 30, 1951, she developed right-sided hemiplegia with aphasia. Examination on readmission to hospital revealed no change of her masculinizing syndrome. She had however in the meantime developed frank diabetes. The urinary excretion of 17-KS was still raised (Fig 2).

The following year the hemiplegia subsided though not completely, but the aphasia persisted unchanged. Her diabetes, which was stable, was treated with 44 units of zinc protamine insulin a day. During the following 6 years her condition remained essentially unchanged except for the development of clitoral hypertrophy and accentuation of the other signs of virilism.

In 1955 a cortisone suppression test was performed (Fig 2). This depressed the 24-hour excretion of 17-KS from 47 mg to 32 mg, of DHEA from 10.3 mg to 7 mg and of 17-ketogenic steroids (17-KGS) from 10 mg to 4 mg. Laparotomy was considered contra-indicated by her hemiplegia.

In August, 1958, the patient suddenly became worse with signs of a new encephalomalacia. She died on August 11, 1958.

Autopsy findings. The most salient changes were found in the pelvic region. The left ovary had been replaced by a lobulated, soft, yellow man-d[illegible]ed mass (Fig 3). The cut surface was brown-yellow and partly haemorrhagic. Similar tumour masses were also observed elsewhere in the pelvic region, in the mesentery and on the surface of the gall bladder. The right ovary was small and fibrotic. The left adrenal weighed 9 g and showed a broad, gyrated cortex. Arteriosclerosis was generalized and most



Fig. 3. Ovarian tumour (cut surface). Small left ovary. Multiple small metastases on peritoneal surface.

pronounced in the cerebral and coronary vessels. The basilar artery contained a thrombus. An area of old encephalomalacia was found within the left hemisphere and multiple recent ones within the occipital lobes and in the cerebellum. The myocardium showed signs of old and recent infarcts.

Microscopical examination. The left adrenal showed nodular hyperplasia. Section from various portions of the ovarian tumour exhibited essentially the same architecture. The tumour was made up of round or polygonal cells arranged in columns, rounded clusters or scattered diffusely and supported by a delicate vascular stroma (Fig. 4). The cellular arrangement closely resembled that of normal adrenal cortex. The cells were well defined and of moderate size with acidophilic granular or vacuolated cytoplasm and with rounded well-demarcated nuclei (Fig. 5).

Special stains for lipids demonstrated considerable amounts of such substance in many cells (Fig. 6). In some parts of the tumour the cellular picture was fairly uniform, in others it was irregular with pronounced cell polymorphism and hyperchromatic nuclei of varying size. Mitoses were rare. Peripheral parts of the tumour contained normal ovarian stroma with several corpora albicantia (Fig. 7). The tumour extended to the vicinity of the large hilar vessels (Fig. 8). The metastases showed the same histological picture as the primary tumour.

The acidophil and chromophobe cells of the anterior pituitary were [illegible]



Fig 4 Hæmatoxylin-eosin × 120

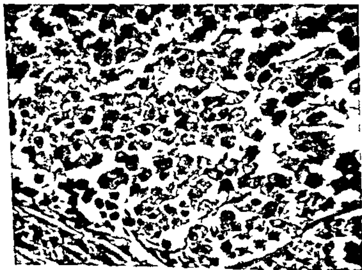


Fig 5 Hæmatoxylin-eosin × 300

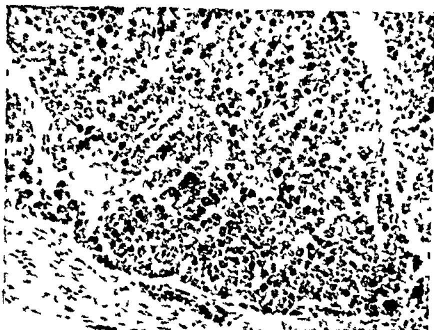


Fig. 6 Scharlach R × 1x

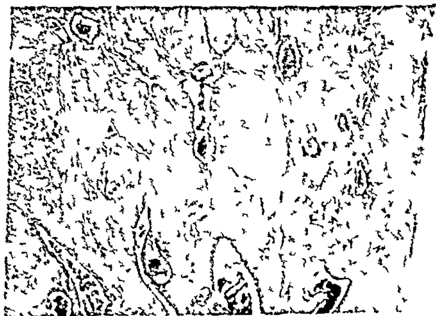


Fig. Haematoxylin-eosin × 30



Γ ₙ 8 Hæma oxyl n-eos n × 3

no mal ppea ance The ba ph l cell appe ed fa ly num rous some were acuol zed n the cytopla m and a few hyal n zed The thyroid showed a m ll g e w h nodule of the collo d type The p n eas showed no d f n e chan es

Con e ts Th s pat ent re ented a rat er cl aracter stic p cture of a r l z n s ndrome th defem n sat on and later ma cul ne hal tu and mu cular de elopment l pertl r cho male t pe of a r gro th tl temporal rece s on at tl e l a r l ne and lo p t l e l o ce \ u ual tl e cl n cal feature of the v ril z ng syn lrome d d not all de elop at the same t me Hypertroph of the l t r atrophy of the l re ts and male type of pub c ha r d str l ut o appeared late Tl e pat ent al o had certa n feature ugge e f Cu h ng s ndrome such a d al etes mell tus hyperten an l ot es t Su l s mptom are not uncommon n adrenal e t tumours of tl e o ar (Kepler Dockerty and Priestley 44) a l len re en tl ey are l elpful n cl n cal l fferentiat on f m ar l enol la toma (Merivale and Forman 1951) De p te le l ng line there a no o teoporo s l ut n tead general zed eo lero Tl n a l a e been due to the ncrea e l androgen

production. The patient thus presented a characteristic virilizing syndrome with certain symptoms typical of Cushing's syndrome, as is sometimes seen in adrenal rest tumours.

Discussion

The most common virilizing ovarian tumour is the arrhenoblastoma, of which more than 150 cases have been reported (Brocq *et al.* 1955). The rest of the masculinizing ovarian tumours, to which the neoplasm in our case must be assigned, are generally classified under the comprehensive term "virilizing lipoid cell tumours", owing to lack of agreement on the histology and histogenesis of these tumours. This divergence of opinion is reflected by the confusing multiplicity of names used by various authors: masculinovoblastoma, ovarian hypernephroma, yellow tumour of the ovary, luteoma, luteinoma, paraluteinoma, luteoblastoma, lutein cell blastoma, luteinized granulosa-theca cell tumour, adrenal (-like) ovarian tumour, adrenal (cell) rest tumour of the ovary, adrenal cortical cell tumour of the ovary, adrenal cortical carcinoma of ovarian origin, adrenal cortical inclusion, androblastoma diffusum and hilus (Leydig) cell or sympathicotropic cell tumour of the ovary, etc.

As to the histogenesis of these tumours, only that of the hilus cell tumour is well defined and well documented. The cells are morphologically and probably even physiologically identical with the Leydig or interstitial cells of the testis, particularly evident because of the presence of the crystalloids of Reinke. The other synonymous names enumerated above refer to tumours of obscure histogenesis. Those are androblastomas, adrenal rest tumours and lutein cell tumours [luteinized granulosa-theca cell tumours and genuine lutein cell tumours, the latter with supposed origin from corpus luteum, luteinized theca interna or ovarian (cortical) stroma].

It is widely believed that the virilizing lipoid tumours are not all of the same origin. On the basis of his comparative studies on testicular and ovarian tumours, however, Teilum (1958) claims to have found transitional stages between androblastomas of the usual type (Sertoli-Leydig cell tumour) and adrenal-like struc-

tures He therefore suggested that lipoid cell tumours and thus adrenal like tumours should be regarded as a variant of arrhenoblastoma (androblastoma diffusum) with development of Leydig cells only Consequently Teilum doubts the existence of adrenal rest tumours This opinion has been assailed by Marchetti and Lewis (1952) Novak (1953) and others who maintain that Teilum is generalizing on the basis of isolated cases

Origin from ectopic adrenal tissue is theoretically possible Owing to the intimate embryological relations between the adrenal cortex and the ovarian medulla one might imagine the tumour to arise from ectopic adrenal tissue Many authors refuse to believe in the existence of ovarian adrenal rest tumours owing to the rare occurrence of aberrant adrenal cortex tissue in the ovary But though adrenal rests may be rare in the ovary they are often seen in the immediate neighbourhood of the gonads (Meyer 1931 Sternberg 1949 Lees and Paine 1958 Bishop 1960)

How should the present case be classified? The lipoid ovarian tumour was seen in an old woman with several years history of marked virilization All the tumour masses more or less resembled adrenal cortex Morris and Scully (1958) however who had the opportunity of investigating more than 20 such adrenal like tumours claim that the histological picture *sometimes* allows of a more specific diagnosis In our case there were no crystalloids of Reinke or perineural arrangement of the cells suggestive of hilus cell tumour Moreover the cells were rather large and clear Lipoid cell tumours originating from lutein cells should presumably show transition from fusiform theca like cells to large polyhedric adrenal like cells together with obvious signs of progesterone production The only well documented case that seems to satisfy these criteria is that of Twombly (1946) Although lutein cells like hilus (Leydig) cells can elaborate androgenically active substances there is no evidence in favour of lutein cell genesis in our case On the other hand in many respects the gross and microscopical appearance of the growth resembled that of adrenal tissue and was in line with the opinion of Novak (1953) when he stated In the majority of this group the constituent cells of the tumour are so typically adrenal in morphology and arrangement that one can scarcely doubt their adrenal nature In

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even malignant adrenal tumours It is possible that the oestrogen deficiency occurring in association with the menopause might have contributed to the malignant nature of the tumour

In the present patient the urinary DHEA was constantly elevated Even during cortisone therapy the excretion of DHEA did not return to normal Bauer and Karl (1952) reported a raised excretion of DHEA in their case while Merivale and Forman (1951) and Engel *et al* (1953) found the DHEA to be normal

In a case of masculinovoblastoma Cagan and Wolff (1957) observed a decrease of the urinary 17 KS from 121 to 63 mg/24 hours during administration of cortisone for 4 days In the present case the cortisone suppression test resulted in a decrease of the 17 KS from 47 to 22 mg/24 hours and a decrease of the 17 KGS from 19 to 4 mg/24 hours The findings may be interpreted as a satisfactory inhibition of that part of the steroid excretion governed by the anterior pituitary The larger relative depression of the 17 KGS than of the 17 KS thus suggested the presence of autonomous adrenal tissue most likely of tumour origin The findings in the DHEA fraction discussed above were also in keeping with such an assumption

The pregnanediol excretion may be elevated in some cases of virilizing lipoid cell tumours (Merivale and Forman 1951 Cagan and Wolff 1957 Lees and Paine 1958) In the present patient the pregnanediol excretion was raised but fell to a low level on administration of cortisone It is thus likely that the pregnanediol originated from the remaining adrenal gland rather than from the tumour Moreover the urinary excretion of 17 KGS also decreased during the administration of cortisone which suggested that this fraction was produced by the normal adrenal gland

The ovarian tumour thus probably produced only androgens As androgens do not appreciably inhibit the production of ACTH there was no reason why the remaining adrenal should become atrophic in this patient as it often does in patients with adrenocortical tumours Why it became hyperplastic is not clear but this appears to occur in 15 per cent of all patients with virilizing ovarian tumours (Sohval 1956)

our opinion there was no evidence to classify the tumour as ar rhenoblastoma (*androblastoma diffusum*) *On morphological and histogenetic grounds the tumour was therefore regarded as a malignant virilizing, adrenal rest tumour of the ovary*

The urinary excretion of the various steroid fractions is given in Fig 2 The initial steroid studies showed an increased excretion of 17-KS We have not been able to find any previous reports on the excretion of 17-KS in malignant, metastasizing virilizing adrenal rest tumour of the ovary but in the benign or possibly locally malignant type of this tumour it is either increased (Kepler *et al* 1944, Winsauer and Manning 1949 Hallett and Holler 1953 Cagan and Wolff 1957) or normal (*Mortell 1949, Michaelsson 1950 Lees and Paine 1958*, and others)

The DHEA fraction of the 17 KS was somewhat elevated The amount of DHEA was about 12 per cent of the total 17 KS It was thus within the range observed in adrenal hyperplasia but less than that often found in adrenocortical tumours

After unilateral adrenalectomy the excretion of 17 KS fell and did not return to the pre-operative level for 5 months When steroid excretion was studied again in 1955 and 1956 the DHEA level was higher than before Since DHEA is known to originate from adrenal tissue and to be increased in patients *with adrenocortical tumours* particularly if malignant in the present case there was reason to suspect the presence of a tu*mour consisting of adrenocortical cells* It also seemed probable that the tumour now produced more androgen than previously an assumption strengthened clinically by *the hypertrophy of the* clitoris and increased facial hirsutism (by this time the patient had to shave daily) *It is* tempting to assume that this patient originally had a benign adrenal like tumour in the ovary which had become malignant and that the growth and its malignant course had been favoured by the early menopause

In this patient the menopause occurred at the age of 39 It is difficult to say whether this should be regarded as a normal variant or as the very first manifestation of the virilizing syndrome Furthermore in view of the finding by Woolley (1958) in animals that oophorectomy favours later development of

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The present case is rather unique in that the natural course of the disease could be followed. Adrenal virilism was initially suspected and unilateral adrenalectomy was performed by the posterior approach. The operation produced a temporary depression of the 17-KS but had no effect on the virilism. Subsequent encephalomalacia contra-indicated laparotomy. This case thus shows how important it is in a given case of virilization to ascertain, as far as possible before operation whether the causal lesion is located in the ovary or the adrenal. If it cannot be located pre-operatively, laparotomy should be preferred to the posterior approach because both ovaries and adrenals can be examined.

The cortisone suppression test produced a larger relative depression of the excretion of 17-KGS than of the 17-KS in our patient. This was interpreted as arguing for the presence of a tumour. At autopsy a tumour originating from the ovary was found. Virilism in association with certain symptoms of Cushing's syndrome, as well as the hormonal findings made a diagnosis of adrenal rest tumour most likely. The histological appearance of the tumour supported this diagnosis.

SUMMARY

A description is given of the clinical course and autopsy findings in a typical case of a virilization syndrome in association with diabetes mellitus, hypertension and osteosclerosis. The patient, who was 72 years at death, was followed for 16 years, probably during the entire course of the disease, during which hormone analyses were performed on several occasions. The findings at complete autopsy supported the diagnosis of malignant adrenal rest tumour of the ovary. Raised urinary excretion of total neutral 17-ketosteroids, dehydroepiandrosteron and pregnanediol had initially suggested an adrenal origin. A corticosteroid suppression test indicated that this test may sometimes be useful in the pre-operative differentiation of adrenal rest tumours from other virilizing ovarian tumours.

g habt und während der letzten Monate hatte ihr Bauchumfang deutl ch zugenommen Der e nwe ende Arzt hatte Asc tes konstat ert und glaubte einen Ovar altumor palp eren zu konnen

D e v e tere Anamne e ergab nichts Besonderes Im Alter von 33 Jahren hatte s e e ne Append c t s und wurde oper ert ansonsten war sie n e in e nem Krankenhaus aufgenommen gewesen und hatte auch sonst ke ne ernst haften Erkrank ngen durchgemacht S e hatte 4 normale Entb ndungen d e letzt m Alter v n 3 Jahren D e Menopause war im Alter von 46 Jahren e ngetreten und se th r hatte s e keinerlei Beschwerden von den Geschlechts rganen gehabt.

Bei der Aufnahmeuntersuchung fand man e ne magere be nahe kachekt sche I ra D e Untersuchung der Brustorgane ergab normal Verhaltn sse fur da Herz e nschl essl ch EKG und Grossenbest mmung m t Rontgen jedoch uf der rechten Seite e nen deutl chen Pleuraerguss der auch im Rontgen er f z ert wurde D e Untersuchung der Bauchorgane ergab deutl che Ze chen fur Asc tes jed ch waren d e Bauchorgane gut zu palp eren, da d e Ba ch wande n cht straft gespannt waren. D e gynakolog sche Untersuchung ergab a f d r rechten Seite ke nen s cl eren patholog schen Befund auf der l nken Seite fand man e nen mannsfaustgrossen Ovar altumor Bere ts n d esem Stad m wurde der Verdacht auf Me gs Syndrom ausge prochen obwohl d e pra perat v vorgenommene Pleurapunkt on 1,500 ccm sangu nolente Fluss g k t ergeben hatte

Be d r Operat on fand man nach der Entfernung von 2 ½ L tern sangu nolentem Asc tes das l nke Ovar um n e nen mannsfaustgrossen Tumor um gewandelt, der an e n gen Stellen der Oberflache e n unregelma s ges blumen kohlahnl ches Aussehen hatte und som t makroskop sch auf Karz nom ver dacht g war Das rechte O ar um war n e nen huhnere grossen Tumor m t glatter Oberflache umge vandelt. In der Ba chhohle fand man ke nerle Ze chen on Metastasen D e Operat on bestand n e ner doppelseit gen Salp ngo- phorektom e welche techn sch le cht war nd der postoperat ve Verlauf war v llkommen kompl kat onsfrei

D e h stolog sche Untersuchung der Praparate (I r f Santesson) zeigte ke nerle Verdacht auf Ma gn tat D s l nke Ovar um war au e ner Struma ar nd Dermo dzyste welche schle mproduz erendes Zyl nderep thel und Talgdrusen enth elt zusammengesetzt das rechte Ov r um led gl ch in e ne Dermo dzy e ohne Struma ovar umgewandelt

SUMMARY

Th i a ca e of Meigs syn lrom originating from truma arı There ha been no recurrence of the serosanguinous hydro thorax an l ascites after the exstirpation of the tumour Pre viou ly only 5 uch cases have been reporte l

Zellner Karl E. Acta obst. et gynec. Scandinav. 40, 40, 1961

Aus der Frauenklinik des Lanslasaretts Sundsvall (Primarius Sven Ingell)
Schweden

MEIGS SYNDROM UND STRUMA OVARII

VON

KARL E. ZELLNER

Seitdem Meigs das später nach ihm benannte Syndrom im Jahre 1934 beschrieben hatte, wurde Meigs Syndrom auch im Zusammenhang mit anderen gutartigen soliden Ovarialtumoren als Fibroma ovarii beschrieben. Meigs (1954) hat selbst in einer Zusammenstellung von 122 Fällen von Meigs Syndrom 2 Fälle beobachtet, welche durch Struma ovarii hervorgerufen worden waren. Dalgaard und Wetteland (1956) berichten über 2 weitere Fälle, darunter einen eigenen. Brocq (1959) beschreibt in seiner Monographie über Struma ovarii 31 Fälle von Meigs Syndrom, verwendet aber dabei die von Funck Brentano (nach Meigs 1954) vorgeschlagene französische Nomenklatur, wobei auch Fälle, welche nur Ascites oder Hydrothorax als Komplikation eines Ovarialtumors aufweisen, als Meigs Syndrom bezeichnet werden. Wie bereits Dalgaard und Wetteland (1956) hingewiesen haben, erfüllen diese Fälle nicht die Forderungen, da bei ihnen lediglich Ascites als Komplikation der Struma ovarii auftrat. Boulard (1958) hat jedoch einen weiteren Fall von echtem Meigs Syndrom ausgehend von Struma ovarii veröffentlicht.

Wir hatten Gelegenheit, einen Fall von Meigs Syndrom bei Struma ovarii zu beobachten.

Krankengeschichte

Eine 63 Jahre alte Frau wurde auf die hiesige Abteilung eingewiesen. Sie hatte bereits einige Jahre hindurch leichte, unbestimmte Bauchbeschwerden

Cronqvist M and Kullander S., Acta obst et gynec Scandinav 40 43 1961

From the Department of Obstetrics and Gynæcology (Professor Alf Sjövall)
Lund Sweden

THE EFFECT OF ENOVID A SYNTHETIC 19-NOR-STEROID (NORETHYNODREL) ON POST-MENOPAUSAL VAGINAL AND UTERINE MUCOSA

BY

M. CRONQVIST AND S KULLANDER

In recent years much interest has been focussed on a group of synthetic steroids of so called 19 nor (no radical at C^{19}) type The se steroids have a mild œstrogenic and a strong progestogenic effect Nor ethynodrel (17α ethynyl 17 hydroxy 5 (10)-œstron) belongs to this group and is the main component of Enovid tablets *

Norethynodrel is said to have a beneficial effect on menstrual disorders (amenorrhœa menorrhagia metrorrhagia) and has also been used in the treatment of endometriosis premenstrual tension and habitual abortion (Proceedings of a Symposium on 19 Nor Progestational Steroids 1957) A search of the literature failed to reveal any reports of clinical trials with this type of treatment in Scandinavia

Norethynodrel can induce the characteristics of the secretory phase in the endometrium of women of child bearing age The response to the steroid is said to be so strong that the endome trium may assume the picture of a predecidua or decidua accord

* Enovid tablets (10 mg) were supplied by courtesy of Searle and Co Chicago The tablets contain 9.85 mg norethynodrel whose œstrogenic effect is potentiated by 0.15 mg ethinyloestradiol 3 methyl ester (a weak œstrogen comparable to œstron)

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Table I *Age Distribution*

Years	40 49	50 59	60–69	70 79	No of Cases
Treated with A tablets (placebo)	2	8	11	3	24
Treated with B tablets (Enovid)	1	10	7	1	19
Total	3	18	18	4	43

Table II *Patients Classified According to Interval since Onset of Menopause*

Years	2 4	5 9	10 14	15 19	20	No of Cases
Treated with A tablets (placebo)	5	6	4	5	4	24
Treated with B tablets (Enovid)	2	9	4	2	2	19
Total	7	15	8	7	6	43

the endometrium and the vaginal mucosa on the morning of the sixth day in association with the operation for prolapse The biopsy specimens were fixed in 10 per cent formalin and embedded in paraffin The microscopical sections were stained with hæmatoxylineosin All sections were first routinely examined by the pathologist and then re examined by one of us (S K)

The patients are classified in Tables I and II according to age and interval since the menopause Only patients in whom biopsy specimens from the endometrium and vagina had been studied histologically before and after treatment with the tablets are included

The complete Manchester operation was done in 23 of the 24 patients treated with tablet A and in 17 of the 19 who received tablets B

The rate of healing was judged on the seventh to fourteenth days after operation usually on the eleventh or twelfth day It was then noted whether the edges of the wound in the vaginal mucosa had healed well (+) whether they were somewhat apart (—) or disrupted (o)

ing to the time of treatment in relation to the menstrual cycle. Thus in women with sufficient endogenous œstrogen and treated with 10 mg. Enovid daily from the fifteenth day of the cycle endometrial biopsy on the twentieth to twenty-second days will show the characteristics of the secretory phase, while if the treatment is started on the fifth day, biopsy on the twentieth to twenty-second days will show development of the stroma of the endometrium to give a decidua-like picture resembling that seen in early pregnancy (Proceedings of a Symposium on 19 Nor Progestational Steroids 1957).

It appears that no investigations have been published on the effect of this new, mainly progestogenic steroid on the endometrium in post-menopausal women. Neither has its effect on the histological picture of the vaginal mucosa been studied. The purpose of the present investigation was to investigate the effects of the steroid on the post menopausal uterus and vagina. By testing the steroid on endocrinically healthy post-menopausal women relatively uniform reactions may be expected without interference by the cyclic production of ovarian hormones.

Material and Methods

The effect of Enovid was studied in a so called double blind test. Certain tablets contained 10 mg. Enovid, others 10 mg. placebo. During the investigation the tablets were marked A and B. The patient, the nurse and the doctor were unaware of the composition of the tablets being dispensed. A sealed code with information of the composition of A and B was not broken until the end of the test.

Patients to be operated on in 1958 for utero vaginal prolapse at this Department who had been menopausal for at least two years were treated with A or B tablets. The patients with even record numbers — a total of 35 — received A tablets (placebo), those with odd numbers — total 29 — B tablets (Enovid). This avoided any bias in the series. On admission a biopsy specimen was taken of the endometrium and of the vagina (usually posterior fornix), after which one tablet A or B was given twice daily for 5 days. Tissue specimens for microscopical examination were taken from

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The rate of healing was judged on the seventh to fourteenth days after operation usually on the eleventh or twelfth day It was then noted whether the edges of the wound in the vaginal mucosa had healed well (+) whether they were somewhat apart (—) or disrupted (o)

Table III. *Histological Appearance of Endometrium and Vaginal Mucosa* before Tablets Were Dispensed*

Interval in Years Since Onset of Menopause	2–4	5–9	10–14	15–19	0
Atrophic endometrium	5+*2***	5+6	3+*3*	5+*3*	4+3
Slightly proliferative endometrium	0+*1*	1+*4*	1+*2*		
Atrophic vaginal mucosa	0+0	*3*+*3*	1+*0*	2+*1*	1+[illegible]
Proliferative vaginal mucosa	5+*2*	3+*5*	3+*1*	3+*1*	3+0
Thick vaginal mucosa with pale areas and distinct signs of hormonal activity		0+*1*			

* In 6 cases treated with B tablets the vaginal mucosa was not examined before treatment.

** Italicized figures denote number of patients afterwards treated with B tablets (Enovid).

Results

The results of the investigations of the *histological picture* of the endometrium and vaginal mucosa *before any treatment* had been started (Table III) showed in agreement with the findings of earlier investigators, that a certain œstrogenic activity may persist even a long time after the menopause (Parks, Scheerer and Greene 1958, Randall, Birtch and Harkins 1957, Siegel and Rothe 1957 and others). In the presence of such slight œstrogenic activity the atrophic endometrium (Fig. 1) shows a slightly irregular proliferation (Fig. 2) and there is an increased thickness of the vaginal mucosa as compared with the usual post-menopausal epithelium (Figs. 3 and 4). Not only the stratum germinativum parabasale and spinosum are seen but also the stratum superficiale with large flat cells with pyknotic nuclei. After dissolving glycogen light regions are seen in the cells. In one of the patients who had ceased menstruating six years previously, the vaginal mucosa showed a strong hormonal stimulation (Fig. 5).

The histological picture of the endometrium and vaginal mucosa *after 5 days medication* with tablets A or B compared with the



Fig. 1. Atrophic endometrium (3 years after onset of menopause) before treatment. 5 μ. Hæmatoxylin eosin. × 150.



Fig. 2. Proliferative endometrium (6 years after onset of menopause) before treatment. 5 μ. Hæmatoxylin-eosin. × 150.



Fig. 3. Atrophic vaginal mucosa (21 years after onset of menopause) before treatment. 5 μ. Hematoxylin-eosin. × 150.

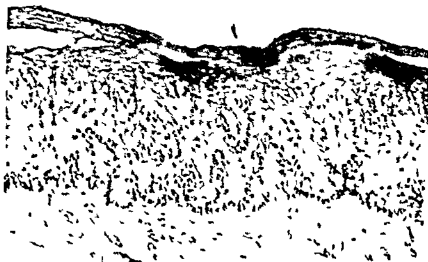


Fig. 4. Proliferative vaginal mucosa (3 years after onset of menopause) before treatment. 5 μ. Hematoxylin-eosin. × 150.



F 5. Vag nal muc s show ng def n e s gns of hormonal s mulat on (6 yea s f er on et of menopause) before treatment 5 u Hæmatoxyl n-eos n × 0

p cture before treatment (Table 4) lo ed that the B tablets (I no d) produced a strong and read ly recogn ed effect (Figs 6—13)

Ho e er even in some of the pat ents ho had received A tablet (placebo) the endometr um sho ed s gns of some hormonal respon e (Fig 14—15) Th re pon e as seen n the f rm of a loo er stroma and a larger number of gland h ch er al ays tra g t an l regular Some of the ep thel al cells of the gl n lular tubules lo ed s ngle m to e The ep thel al cell also ontained abundant c toplasm and had a t mulated appearance (F g 14—15) In some ca e n h ch the vag nal u a ho ed a corre pond ng hormonal react on the epi l lum appeare l to be th cker th pale area

In e eral of the ca e treated th Eno l but n none of the c ntrol gn of secret n ere een n the ep thel um of the en l metr m (F g —8) on et me long after the onset of the



Fig 6 Proliferative endometrium after curettage and 5 days treatment with norethynodrel (8 years after onset of menopause) 5 μ Hæmatoxylin-eosin × 150



Fig 7 Strong proliferation and commencing secretion in endometrium after curettage and 5 days treatment with norethynodrel (5 years after onset of menopause) 5 μ Hæmatoxylin-eosin × 150



Fig. 8 Strong proliferation and commencing secretion in endometrium after curettage and 5 days treatment with norethynodrel (6 years after onset of menopause) 5 μ Hæmatoxylin-eosin × 150



Fig. 9. Proliferative endometrium after curettage and 5 days treatment with norethynodrel (30 years after onset of menopause patient aged 78) 5 μ Hæmatoxylin-eosin × 150

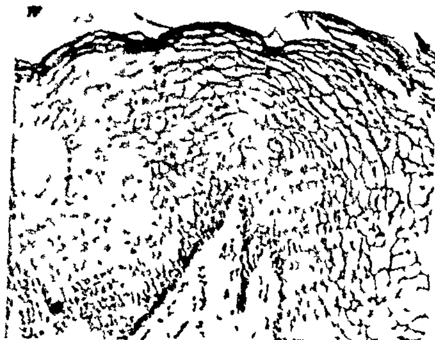


Fig. 10. Thick vaginal mucosa with pale areas — "hormonal activity" — after 5 days treatment with norethynodrel ([illegible] year after onset of menopause) [illegible]. Hematoxylin-eosin × 150

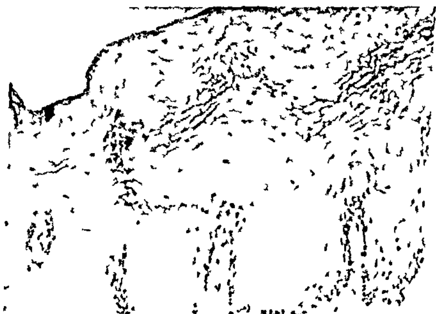


Fig. 11. Thick vaginal mucosa [illegible] pale area — "hormonal activity" — after 5 days treatment with norethynodrel (9 years after onset of menopause) [illegible]. Hematoxylin-eosin × 1[illegible]



Fig. 12 Thick vaginal mucosa with pale areas — "hormonal activity" — after 5 days treatment with norethynodrel (15 years after onset of menopause) 5 μ Hæmatoxylin-eosin. × 150

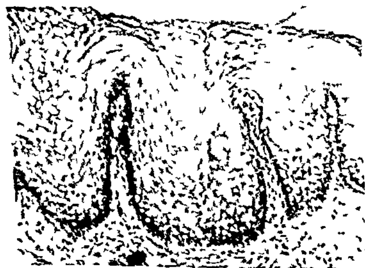


Fig. 13 "Hormonal activity" in vaginal mucosa after 5 days treatment with norethynodrel (30 years after onset of menopause) 5 μ Hæmatoxylin-eosin × 1[illegible]0



Fig 14 Proliferative endometrium after curettage and 5 days treatment with placebo (1 year after onset of menopause) 5 c Hematoxylin-eosin, × 1 0 (cf Fig 3)



Fig 1 Proliferative endometrium after curettage and day treatment with placebo (7 year after onset of menopause) Hematoxylin-eosin × 1

Table IV *Histological Appearance of Endometrium and Vaginal Mucosa after 5 Days' Treatment with A (Placebo) or B (Enovid) Tablets*

Interval in Years since Onset of Menopause	2–4	5–9	10–14	15–19	20
Atrophic endometrium	2+0	3+2	3+1	3+0	2+0
Proliferative endometrium	1+2*	0+5	1+3	1+1	1+1
Strongly proliferative endometrium, signs of "hormonal activity"	2+1	3+3	0+1	1+2	1+2
Signs of secretion in endometrial glands		0+2	0+1	0+2	0+2
Atrophic vaginal mucosa		2+1			
Moderately thick vaginal mucosa	5+1	4+2	4+2	5+1	4+2
Very thick vaginal mucosa	0+2	0+7	0+2	0+2	—
Pale areas in epithelium	1+3	2+9	4+2	2+2	0+2
Very thick vaginal mucosa with pale areas "hormonal activity"	1+2	2+7	1+2	1+2	0+2

* Italicized figures denote cases treated with Enovid.

menopause. The reaction to Enovid varied from one individual to another (Table IV). Norethynodrel given orally thus has a strong progestogenic activity which, probably on the basis of a slight oestrogenic stimulation, may produce a response even in advanced age.

The cases are classified according to rate of healing after operation in Table V.

Thus in 27 of the 35 patients who received tablets A and in 24 of the 29 who received tablet B healing was good. The difference was not statistically significant. Slight infection was sometimes present in those cases in which the wound had not healed completely. Post-operative hæmorrhage, if any, was never severe enough to require intervention.

No side-effects of the medication such as nausea and vomiting as sometimes occurs after the administration of œstrogen were noted.



Fig 14 Proliferative endometrium after curettage and 5 days treatment with placebo (21 years after onset of menopause) Hæmatoxylin-eosin × 1 (cf Fig)



Fig 1 Proliferat e endometri m aft r c urettag and day treatment th placebo (year after n et f men pa e) Hæmat xyl n-eos n × 1

Table IV *Histological Appearance of Endometrium and Vaginal Mucosa after 5 Days' Treatment with A (Placebo) or B (Enovid) Tablets*

Interval in Years since Onset of Menopause	2–4	5–9	10–14	15–19	20
Atrophic endometrium	2+*0*	3+*2*	3+*1*	3+*0*	2+*0*
Proliferative endometrium	1+*2**	0+*5*	1+*3*	1+*1*	1+*1*
Strongly proliferative endometrium, signs of "hormonal activity"	2+*1*	3+*3*	0+*1*	1+*-*	1+*2*
Signs of secretion in endometrial glands		0+*2*	0+*1*	0+*2*	0+*2*
Atrophic vaginal mucosa		2+*1*			
Moderately thick vaginal mucosa	5+*1*	4+*2*	4+*2*	5+*1*	4+*2*
Very thick vaginal mucosa	0+*2*	0+*7*	0+*2*	0+*2*	—
Pale areas in epithelium	1+*3*	2+*9*	4+*2*	2+*2*	0+*2*
Very thick vaginal mucosa with pale areas "hormonal activity"	1+*2*	2+*7*	1+*2*	1+*2*	0+*2*

* Italicized figures denote cases treated with Enovid

menopause The reaction to Enovid varied from one individual to another (Table IV) Norethynodrel given orally thus has a strong progestogenic activity which probably on the basis of a slight œstrogenic stimulation may produce a response even in advanced age

The cases are classified according to rate of healing after operation in Table V

Thus in 27 of the 35 patients who received tablets A and in 24 of the 29 who received tablet B healing was good The difference was not statistically significant Slight infection was sometimes present in those cases in which the wound had not healed completely Post operative hæmorrhage if any was never severe enough to require intervention

No side effects of the medication such as nausea and vomiting as sometimes occurs after the administration of œstrogen were noted

Table V *Classification of Cases according to Rate of Healing*

Interval in Days between Operation and Re-examination	7–8			9–10			11–12			13–14			14 days		
Healing	+	–	o	+	–	o	+	–	o	+	–	o	+	–	o
Cases treated with A tablets (placebo)				1	1		13	5		10	2		3		
Cases treated with B tablets (Enovid)			1	3			13	3	1	7			1		

+, healed well —, gap between edges of wound o edge of wound apart wound disrupted

Discussion

In animal experiments and in clinical trials it has been shown that œstrogens have a beneficial effect on healing of vaginal wounds (Sjöstedt 1953, Sjövall, 1953) Sjövall (1954) suggested that even androgenic substances might accelerate healing of vaginal wounds since the administration of testosterone after the menopause results in a proliferation of the atrophic vaginal epithelium and deposition of glycogen In the present study the moderate œstrogenic and strong progestogenic effect of Enovid with its proliferative effect on the vaginal mucosa did not appear to have any pronounced effect on healing

The signs of "hormonal activity" or "œstrogenic effect" noted in several of the pathologist's reports on routine examination of the endometrium and sometimes also of the vaginal mucosa from the patients treated with placebo might be due to the intervention (complete curettage and vaginal biopsy) performed before treatment was started The newly formed growing endometrium is not in the same resting phase as the endometrium that was curetted the first time Operation might have caused a certain degree of hyperæmia (by release of histamine?) and stimulation of both the uterus and the vagina Neither can it be excluded that a persisting low œstrogen production in post menopausal women might be rhythmical and that the second curettage and vaginal biopsy sometimes happened to coincide with a peak in the fluctuating œstrogen level in the blood It appears clear however that con

trols and preferably the double blind test with placebo must be included in the assessment of the capacity of different substances to stimulate the endometrium and vaginal mucosa Due consideration must also be given to the fact that the reaction to the administration of hormones differs from one patient to another

In no instance did Enovid produce such a decidual stroma as has been observed after prolonged uninterrupted treatment of women of the child bearing age a reaction that can be confused with the histological picture of stromal sarcoma (Dockerty Smith and Symmonds 1959)

In contrast to purely œstrogenic substances norethynodrel thus appears first to produce proliferation of the endometrium and then signs of secretion It thereby has an effect on the inactive endometrium which resembles the development during the menstrual cycle

SUMMARY

The effect of norethynedrol (Enovid) a synthetic progestogenic 19 norsteroid on the endometrium and vaginal mucosa of post menopausal women was investigated by the double blind test on patients to be operated upon for utero vaginal prolapse Twenty nine women received active tablets and 35 placebo tablets daily for 5 days before the operation Norethynedrol produced signs of proliferation and sometimes also secretion in the endometrium and a thick vaginal mucosa rich in glycogen The response varied from one individual to another The effect could be seen more than 20 years after the menopause

A slight stimulation of the endometrium and vaginal mucosa was noted in some of the women who had received placebo The possible cause of this is discussed

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VALUE OF HISTAMINASE AND PREGNANEDIOL DETERMINATIONS IN SUSPECTED ILLEGAL ABORTION

BY

N. E. BORGLIN AND B. WILLERT

In a previous investigation (Borglin and Willert 1957) of the prognosis of threatened abortion as judged by determinations of the histaminase activity of the plasma and excretion of pregnanediol in the urine, it was shown that when both tests give values normal for the stage of pregnancy the prognosis is usually good, and that when the values for the time of pregnancy are below this level the prognosis is, as a rule, poor. In several of the cases in which the histaminase values in the plasma and the excretion of pregnanediol in the urine were normal but in which abortion nevertheless occurred there was clinical reason to suspect criminal abortion. This discrepancy between the results of the tests and the result of pregnancy was tentatively ascribed to the method by which the illegal abortion had presumably been induced. It is probable that the illegal instrumental interference does not damage the placenta, the latter retaining its capacity to elaborate histaminase and progesterone, which it does not on spontaneous abortion.

In the previous investigation the possibility of utilizing this difference in the diagnosis of criminal abortion was discussed. At that time the number of cases available was too small to permit any valid conclusions. The series has in the meantime been extended and analyzed in this respect and the results are given below.

Methods and Material

The histaminase activity of the plasma was determined according to Ahlmark (1944) The results were evaluated in the same way as in the previous investigation (Borglin and Willert 1957) The excretion of pregnanediol *in the urine was determined* by the method of Jensen (1955) apart from a slight modification *during the last two years (Jensen, 1958) When the excretion* of pregnanediol was at least 5 mg a day, the prognosis of the pregnancy was regarded as good

The study was conducted on cases of threatened or incomplete abortion treated at the Department of Gynecology, Malmo General Hospital, during the years 1953 to 1959 in which the histaminase activity of the plasma and the excretion of pregnanediol in the *urine had been determined — a total of 516 cases Since the* histaminase and pregnanediol levels had not been determined in all cases admitted to the Department the series is not representative of the frequency of abortions — spontaneous or procured

The treatment of threatened abortion during the period of investigation was in principle the same, namely complete bed rest vitamin E (100 mg daily) sedatives and large doses of progesterone or preparations with a progestogenic effect This therapy was given until the threat to abort subsided or was considered *inevitable*

Out of the total series those cases were selected in which the abortion *had occurred after known or suspected illegal intervention* (41 cases Group I) In addition all cases were selected in which abortion had occurred despite the fact that the prognosis as judged by the histaminase activity and excretion of pregnanediol had been regarded as good (31 cases Group II) An abortion was suspected as being criminal if the patient had a temperature of 38° C or more on at least two consecutive occasions and if the E S R had been abnormally high for the stage of pregnancy and no good explanation could be offered for the fever or for the raised E S R In addition those cases were regarded as criminal in which the vagina or uterine cervix showed evidence of instru*mental trauma* In the cases of Group II the histories and hospital records gave no reason to suspect criminal intervention

Results

The 72 selected cases are presented in Table I

Table I *Total Series and Selected Cases*

	Total Series	Group I	Group II
1953	45	3	4
1954	60	11	1
1955	63	3	7
1956	101	7	8
1957	88	7	6
1958	98	5	4
1959	61	5	1
Total	516	41	31

Group I included 25 cases in which abortion had occurred despite a favourable prognosis as judged by the histaminase and pregnanediol determinations and 16 cases in which the histaminase and/or pregnanediol determinations suggested a bad prognosis. A total of 56 abortions (25 from Group I and all in Group II) thus occurred in women in whom the pregnanediol and histaminase values were normal for the stage of pregnancy (10 8 per cent of the whole series)

Tables II and III show the age distribution and civil status in the two groups Group I included a large number of fairly young patients 42 per cent (17/41) below 25 years as against 19 per cent (6/31) in Group II In addition Group I included a larger number of patients aged 35—39 namely 24 per cent (10/41) as against 16 per cent (5/31) in Group II The age distribution in Group II was much more even than in Group I (Fig 1) The difference is due mainly to the fact that in Group I there were more unmarried women in the lower age group and more divorced women in the higher This difference agrees well with the assumption that attempted criminal abortion is more common among unmarried and divorced women In that groups as many as 46 per cent (19 41) were unmarried or divorced as against 7 per cent (2 31) in Group II

Closer analysis of Group I showed that of those 16 cases in

Table II *Group I Cases of Suspected Criminal Abortion*

Age in Years	Married			Unmarried			Divorced			Total
	a	b	c	a	b	c	a	b	c	a+b
<20				1	1					2
20—24	5	2		3	4			1		15
25—29	3			1			2			6
30—34	2	3		1						6
35—39	3	3			1		2	1*	(1)	10
40—44	1						1*		(1)	2
Total	14	8	0	6	6	0	5	2	(2)	41

a = Favourable prognosis as judged by the histaminase and pregnanediol values

b = Histaminase and pregnanediol values suggesting poor prognosis

c = Criminal interference admitted (in a or b indicated by *)

Table III *Group II Abortion Despite Favourable Histaminase and Pregnanediol Values Criminal Interference Clinically not Suspected*

Age in Years	Married		Unmarried		Divorced		Total
	d	e	d	e	d	e	d+e
<20							0
20—24	2	3	1				6
25—29	7	3					10
30—34	7	2					9
35—39	2	2			1		5
40—44	1						1
Total	19	10	1	0	1	0	31

d = Spontaneous abortion without known aetiology

e = Verified incompetence of the internal os of the cervix

which the histaminase and pregnanediol determinations had suggested a poor prognosis abortion had probably occurred several days or weeks before admission to hospital in 9 In another of these cases curettage produced only small amounts of necrotic decidual tissue and in a further case there was probably a dead

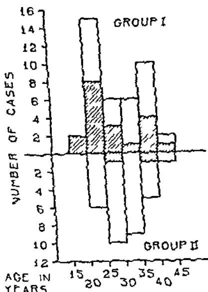


Fig 1 Age distribution of the two selected groups. Shaded areas indicate number of divorced and unmarried women

ovum which had been retained for a long time (missed abortion) in another of the cases abortion was due to poisoning probably by mercury In 12 of these 16 cases the histaminase and pregnanediol determinations could thus hardly be expected to be normal It these 12 cases be excluded it will leave in Group I as many as 60 per cent (25/49) in which abortion occurred yet the histaminase and pregnanediols levels were prognostically favourable

Group II consisted of 31 cases in which abortion had occurred *despite histaminase* and pregnanediol values normal for the stage *of pregnancy* This group included a large number of cases of incompetence of the internal *cervical* The total series of 416 cases included 20 cases of this *type and in* 6 of them pregnancy continued In 4 with low histaminase and/or pregnanediol values abortion occurred and *in the remaining* 10 cases abortion occurred despite favourable histaminase *activity in the* plasma and a pregnanediol excretion in the *urine* of more than 5 mg per day *These*

10 cases thus belong to Group II It is quite natural that in this type of abortion the histaminase determination and excretion of pregnanediol in the urine can be the same as in normal pregnancy In women with cervical incompetence the canal widens and the membranes rupture with escape of the liquor amnii Until the pregnancy has been terminated by labour the placenta is intact and can elaborate normal amounts of progesterone and histaminase The mechanism of this type of abortion may be compared with what is supposed to occur in some methods of criminal abortion The fact that in cervical incompetence we find the same changes in histaminase concentration and pregnanediol excretion strongly supports the idea that these tests can be used as a guide to the diagnosis of criminal abortion

In most cases incompetence of the internal os is easy to recognize even during actual abortion If these cases in Group II are excluded it leaves 21 in which for some unknown reason the abortion occurred despite favourable histaminase and pregnanediol values

The frequency of abortion in our total series was about 52 per cent If cases of cervical incompetence be excluded it will be found that of those cases in which there was no reason to suspect illegal intervention and in which the histaminase and pregnanediol values were normal abortion occurred in only 8 per cent

It may thus be concluded that if criminal intervention is suspected the probability of finding normal histaminase and pregnanediol values is ten times greater than if such intervention is not suspected provided that the abortion is not due to incompetence of the internal os of the cervix

Discussion

In a spontaneous abortion it is assumed that the ovum has been dead long before the actual abortion (Streeter 1931) The placenta then gradually loses its capacity to elaborate histaminase and hormones This provides a possible guide to the prognosis for the pregnancy by determining the levels of histaminase and hormones such as the excretion of pregnanediol and œstrogen in the urine If the placenta can maintain the normal histaminase con

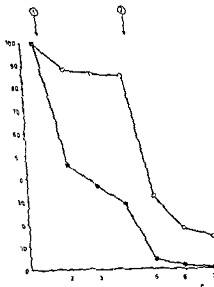


Fig. — A comparison of excretion of pregnanediol (open circles) and of "total" œstrogen (filled circles) before and after artifically induced fœtal death and following complete removal of the placenta and macerated fœtus. The values are expressed as percentages of the pre-operative levels. Arrow 1 indicates the time of interruption of the connections between placenta and fœtus. Arrow 2 indicates the time of complete removal of the placenta and macerated fœtus. The percentages are calculated on ground of geometric mean values. (From Cassmer, O. Acta endocrinol. 32, Suppl. 45, 1959.)

centration in the plasma and if the excretion of pregnanediol is at least 5 mg/24 hours there is usually reason to suppose a good prognosis for the pregnancy.

In a small group, about 20 per cent, this method of judging the prognosis fails. On closer analysis of this group suspected or known criminal interference was surprisingly common and several cases were found to have incompetence of the internal os of the cervix. In both groups one might expect that, in contrast to what occurs on spontaneous abortion, the fœtus and the placenta had not died. Instrumental interference and cervical incompetence produce a similar effect: rupture of the membranes with escape of the liquor amnii but leaving the placenta intact. In the group

of suspected criminal abortion we also found normal histaminase and pregnanediol values in 25 (61 per cent) and among the cases of incompetence of the internal os in which abortion occurred the corresponding numbers were 10/14 (71 per cent) Cervical insufficiency is readily recognized clinically and then histaminase and pregnanediol determinations are unnecessary If criminal interference is suspected the occurrence of abortion despite normal histaminase and pregnanediol values strengthens such suspicion

It has been shown experimentally (Cassmer, 1959) that rupture of the membranes alone does not cause a significant fall in the excretion of pregnanediol in the urine while on removal of the placenta the fall is abrupt (Fig 2) These investigations thus provide further support for the assumption that abortion in women with prognostically favourable histaminase and pregnanediol values could be the result of an illegal operation

SUMMARY

From a series of threatened or incomplete abortion (516 patients) in which the histaminase concentration in the plasma and the excretion of pregnanediol in the urine had been regularly determined cases of suspected or known illegal intervention were selected (Group I 41 cases) as well as cases in which no criminal intervention was suspected and abortion occurred despite a good prognosis for pregnancy as judged by histaminase and pregnanediol determinations (Group II 31 cases)

In 25 of the cases in Group I abortion occurred despite normal histaminase and pregnanediol values In a further 12 cases in this group there was no reason to expect such values (determinations made several days after the abortion or abortion due to poisoning)

If these be excluded the prognosis was regarded as favourable in 86 per cent of the women in Group I yet despite this abortion occurred

In Group II 31 cases in which there was no reason to suspect illegal intervention abortion was often (10 cases) due to incompetence of the internal os of the cervix The remaining 21

cases represented only about 8 per cent of the total series of abortions in the entire series

This means that if the abortion is not due to incompetence of the internal os of the cervix if criminal intervention is suspected clinically and if the histaminase and pregnanediol values are normal the abortion seems to be illegal in 10 out of 11 cases

The histaminase and pregnanediol values in these forms of abortion are probably normal to the method of criminal intervention *per se* This assumption is supported partly by other experimental investigations and partly by the findings in cases of incompetence of the internal os of the cervix

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and Oram (1951) described a complication in one of their cases as follows

A small opening was seen in the cervix uteri just above the intact os Abortion had apparently occurred through this opening Evacuation of the uterus was performed through the opening The lesion was caused by a vulsellum forceps

Two days previously puncture of the ovum had been done but the cervical lesion was not observed until the subsequent evacuation However the authors did not report whether the lesion was found in the anterior or posterior wall of the cervix nor did they state where the vulsellum forceps had been placed during the primary intervention but it is likely that the lesion was of the same type as those described below

The lesions consist of large irregular more or less transverse ruptures in the posterior wall of the cervix *downwards separated* from the external os by a tissue bridge which is from 1 to 3 cm wide and upwards bounded by the *posterior fornix*

In the present series rupture occurred in patients in whom abortion had been induced either by *injection of soap (cremor saponis)* or by puncture of the ovum One or two days later when the patient came to the operating theatre for *evacuation of the uterus* it was seen that the external os was intact while there was a large rupture in the posterior wall of the cervix *through* which abortion had occurred

In the autumn of 1958 a patient was admitted to the State Maternity Hospital for Jutland in incipient labour about two months before term On closer examination it was found that delivery was going to occur through a large rupture in the posterior wall of the cervix It was then revealed that an *abortion* had been induced by *injection* of cremor saponis 18 months previously and that a rupture of the type just described had occurred during the intervention Shortly *afterwards* I encountered a similar rupture in the posterior wall of the cervix in another patient in actual labour In this patient an abortion had been induced two and a half years previously by puncture of the *ovum*

After having encountered these two ruptures I reviewed the case records on *induced* abortions performed in the Department of Surgery K Aarhus Municipal Hospital

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CENTRAL SPONTANEOUS RUPTURE OF THE CERVIX UTERI

A Complication of Induced Abortion

BY

TORJUS SKAJAA

Gynecologists and surgeons have always been greatly interested in the complications of induced abortion and many types of these complications have been reported during the years

From the beginning of this century up to about 1930 several cases of what has been called central cervical rupture have been described by German investigators (Blumenreich 1907 Bublitschenko 1925 Caffier 1928 Hiess 1920 Sahler 1926 Seitz 1946 Wiczynski 1919) Thus Caffier published an excellent survey on this subject in 1928 and the complication has also been mentioned by Seitz and Amreich (1946)

In the German series the lesion is mentioned as a consequence of criminal, spontaneous and what is of the greatest interest in this connexion induced abortions The abortions concerned were induced either by laminaria dilatation according to the method of Hegar or other methods

However as far as I have been able to trace central cervical rupture or — as I have chosen to call it — central spontaneous rupture of the cervix uteri has not been described as a complication of induced abortion in the Danish medical literature (Frolle 1950 Ostergård 1956 Berthelsen and Ostergård 1958 la Cour and Gaunt 1959) In a paper on the complications and mortality in induced abortion Fabricius Møller

and Oram (1951) described a complication in one of their cases as follows

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Fig. 1. Distribution of the Spontaneous Ruptures of the Cervix Uteri in the Present Series

	Total	Primigravidae <21 Years	Rupture
Induced abortion	214	34	
Puncture of the ovum	34	9	3
Cremor saponis	161	25	1
Cremor saponis and puncture of the ovum	19		2

During the period from 1st January, 1956 to 31st July, 1958, abortion was induced in 214 patients in this Department. The case records revealed a total of 6 cases of spontaneous rupture of the cervix uteri. The present series also includes a case with the same complication in which the intervention had been performed in another hospital.

As already mentioned, 6 of these 7 cases of central spontaneous rupture of the cervix uteri originate from a basic series consisting of 214 cases of induced abortions. In 161 cases the abortion was induced by injection of soap (cremor saponis) and in 34 cases by puncture of the ovum. In the remaining 19 cases injection of cremor saponis proved ineffective and was therefore followed by puncture of the ovum. In both methods the directions given by Fabricius-Møller and Oram (1951, 1952) and Oram (1948, 1949, 1951, 1956) were closely followed (Fig. 1).

Spontaneous cervical rupture occurred in 3 patients after puncture of the ovum, in 2 after injection of cremor saponis and in 2 in whom injection of cremor saponis was followed by puncture of the ovum.

The 7 patients with rupture of the cervix uteri were all under 21 years at the time of the intervention and they were all primigravidae. Their average age was 17 years.

The lesions were all large, irregular, more or less transverse tears in the posterior wall of the cervix, but the external os was intact. All 7 aborted through the rupture and the ensuing evacuation of the uterus was also performed through the rupture. Only

in Cases 2 and 7 (Fig 2) did appreciable bleeding occur from the lesion In these two cases the rupture was therefore sutured while it was allowed to heal spontaneously in the remaining 5

All the patients were treated with antibiotics When fever occurred this was only of short duration The average length of the hospital stay was nine and a half days

In all 5 cases in which puncture of the ovum was done the operations were performed by the same experienced surgeon Dilatation by the method of Hegar was not performed in any of the cases As a point of interest it may be mentioned that the first three ruptures occurred within the space of nine days

All 7 patients with spontaneous rupture of the cervix uteri were re examined in the autumn of 1958 *i e* from fifteen to thirty months after the rupture

Figure 2 shows the results of the follow up examinations It appears that 3 of the patients had not been pregnant since the abortion in 1956 At the follow up 2 of these revealed a fibrous thin area in the posterior wall of the cervix at the site of the healed rupture On the other hand the third patient had since the abortion had distinct abdominal reactions with pain discharge dyspareunia and fever Physical examination revealed slightly bleeding granulation tissue surrounded by fibrous tissue at the site of the old rupture It is possible that these findings may explain some of her complaints

Three patients had borne children after the abortion 2 at term and the third about two months prematurely In 2 of these 3 a *tissue bridge* was seen across the presenting head at a late stage of labour both the os and the area previously involved in the rupture showed progressive dilatation during the first stage of labour

In one of the patients (Case 6) the abortion induced in 1956 had been followed by three late spontaneous miscarriages and during the same period the patient had suffered from abdominal pain vaginal discharge and dyspareunia Physical examination revealed pronounced fibrous and cicatricial changes at the site of the rupture Hysterography showed no abnormalities specifically the isthmic region appeared to be normal However as the internal os admitted a Hegar No 10 the cause of the subsequent abortions may have been insufficiency of the isthmus

Fig. 2 Evaluation of the Results at the Follow up Examination

No	Age	Gestation in Weeks	Method	External Os	Later Pregnancies	Complications	Follow up
1	20	16	Cremor saponis	0 cm	0	0	
2	15	16	Cremor saponis and puncture of the ovum	3 cm	0	0	
3	15	15	Cremor saponis and puncture of the ovum	0 cm	0	Pain discharge, dyspareunia fever	
4	13	20	Puncture of the ovum	0 cm	1 normal delivery	0	
5	16	12	Puncture of the ovum	0 cm	1 delivery with →	Re-rupture 0	
6	20	20	Puncture of the ovum	0 cm	3 abortions	Pain discharge dyspareunia	
7	15	12	Cremor saponis	0 cm	1 delivery in the 7th month	Pain discharge dyspareunia	

Before the causes of the ruptures are discussed I wish to summarize the points which are definitely known in regard to the ruptures

All the patients were primigravidæ and all were under 21 years The duration of the pregnancies varied from twelve to twenty weeks The external os was intact the site of the rupture being the posterior wall of the cervix in all cases Both at the time of the rupture and at the follow up it appeared that the lesion was situated below the isthmic region It also seems to appear from the case records that these patients had more intense pains during abortions than is usually experienced Dilatation was not performed in any of the cases

These facts are in complete agreement with the data given in the German reports In these cases the rupture was also found in the posterior wall of the cervix and occurred after abortion in the third to the sixth months of pregnancy in young primigravidæ In one series (Ottow 1925) consisting of 21 cases of spontaneous rupture 19 of the patients were primigravidæ and 13 were under 25 years

In another series from the University Clinic of Vienna (Sahler 1926) the frequency of this lesion was reported to be 1 1 000 According to the present case material the lesion should be far more frequent — 6 ruptures among 214 patients in whom abortion was induced *i e* about 1 35

The German authors (Wiczynski 1919 Ottow 1925) expressed the view that the lesion is ushered in by a cervical abortion Stenosis of the external os elongation of the cervix anteflexion of the uterus or infantile genitalia result in marked distension of the cervix uteri leading to a tear in this area The rupture is always transverse

The German authors believe that with the exception of spontaneous ruptures observed after criminal abortion (Ottow 1925) it can be excluded that instrumental lesions or other forms of external violence could be responsible for the ruptures (Hess *1920*) I find that these causes can also be definitely ruled out in the present series Dilatation or any other instrumental intervention was *not* performed prior to the injection of cremor saponis

The present cases of spontaneous rupture of the cervix uteri

following induced abortion seem to lend support to the assumptions that the lesion is referable to inelasticity of the external os and that it occurs in the posterior wall because of the anteflexion of the uterus.

As shown in the case reports, spontaneous rupture of the cervix uteri may give rise to severe discomforts persisting for many years after the occurrence of the lesion. In the German series many cases are reported in which a permanent fistula developed through which the patient menstruated, aborted or bore children (Wiczynski, 1919, Caffier 1928).

It is possible that spontaneous rupture may be prevented if this complication is borne in mind when a patient has very vigorous and painful uterine contractions prior to the abortion. If, under these conditions, a gynaecological examination reveals signs of cervical abortion, it will be reasonable to use vigorous dilatation of the external os. In view of the high frequency of cervical ruptures observed in the present series, it must be recommended that a careful gynaecological examination (inspection) is performed before young primigravidae are discharged from hospital after induced abortion.

Primary suture was performed only in 2 of the patients in the present series, while the rupture was allowed to heal spontaneously in the remaining 5 cases. However, this leads to greater fibrous and cicatricial changes than when suture has been done. It can hardly be doubted that these ruptures should be repaired by primary suture. If the lesions pass unrecognized at first, plastic operation may be indicated, especially if discomforts have been present.

Summary and Conclusions

Seven case of so called spontaneous central rupture of the cervix uteri complicating induced abortion are described. This lesion does not seem to have been described in the Danish medical literature, whereas many cases have been reported by German authors. In a basic series of 214 cases of induced abortion, this followed injection of cremor saponis in 176 cases, in which two ruptures occurred. Puncture of the ovum was performed in 36 cases, in

cluding 5 in which a central rupture of the cervix occurred The lesion was seen only in young primigravidæ

In the present series these spontaneous central ruptures of the cervix uteri do not seem to be due to instrumental lesions afflicted during the primary intervention The view is expressed that the rupture occurs when the external os is relatively inelastic and when — possibly due to this inelasticity — a cervical abortion is present The localisation of the rupture in the posterior wall of the cervix is assumed to be due to anteflexion of the uterus

The lesion may give rise to late complications in the form of chronic abdominal reactions repeated abortions premature births and cervicovaginal fistulæ For these reasons the following measures should always be taken

(1) The patients should be examined with a special view to cervical abortion if the uterine contractions are very painful especially in young primigravidæ Vigorous dilatation of the external os may prevent rupture

(2) The same group of patients should be subjected to a careful gynæcological examination (inspection) before their discharge from hospital

(3) When spontaneous rupture is recognized after abortion the lesion should be sutured at once In lesions which escape recognition after abortion plastic operation may later be indicated

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GENITAL PROLAPSE

Review of 443 Surgically Treated Cases

BY

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Surgical treatment of prolapse was rarely practised before the middle of the 19th century. Present methods are based on principles from the latter half of the 19th century and the first decade of the 20th.

Originally methods were limited to excision of the mucosa of the anterior and posterior vaginal walls or alternatively amputation of the cervix in those cases where it was hypertrophied or prolapsed. Even before the turn of the century however Archibald Donald (1908) of Manchester had combined *colporrhaphy* and amputation of the cervix in the procedure which has ever since been known as the Manchester *operation*. It was subsequently modified especially by Fothergill *(1921)* and Shaw (1934) and gradually it has become the most common prolapse operation described in the Anglo-American and Scandinavian literature (Solomons 1955, Danielson 1957, Gordon and Gordon 1957).

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GENITAL PROLAPSE

Review of 443 Surgically Treated Cases

BY

JENS J JACOBSEN THORKILD FREDERIKSEN AND F KJELD NIELSEN

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Originally methods were limited to excision of the mucosa of the anterior and posterior vaginal walls or alternatively amputation of the cervix in those cases where it was hypertrophied or prolapsed Even before the turn of the century however Archibald Donald (1908) of Manchester had combined colporrhaphy and amputation of the cervix in the procedure which has ever since been known as the Manchester operation It was subsequently modified especially by Fothergill (1921) and Shaw (1954) and gradually it has become the most common prolapse operation described in the Anglo American and Scandinavian literature (Solomon 1955 Danielson 1957 Gordon and Gordon 1957)

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In 1898 Watkins described vesico-vaginal interposition of

the uterus in the treatment of cystocele The following year Wertheim (1899) published his results obtained by a similar operation The latter was modified by Schauta (1903) and is still in use, with modifications, in a number of Scandinavian and American hospitals (Andersen 1948, Brady, 1953 Nilsen, 1954, Kristoffersen, 1955)

Vaginal hysterectomy was also utilized in the treatment of uterine prolapse as early as the last decades of the 19th century Combined with colporrhaphy and suspension of the vagina it is still widely used in the U S A (Phaneuf 1950, Counseller, 1953, Tyrone 1957), although in Scandinavia it is considered to be of little value (Bach Nielsen and Stakemann 1957)

In the early years of the present century *fixation of the uterus to the abdominal wall* was introduced It was sometimes used as *the sole method* of treatment of uterine prolapse and sometimes as a supplement to colporrhaphy The most common method was *Kocher's ventrofixation* suturing the uterus to the anterior abdominal wall After Engstrom's and Essen Moller's results of combined colphorrhaphy and ventrofixation had been submitted by Boije and Olow respectively at the Scandinavian Congress of Surgeons in Copenhagen 1913 this method was in common use in Scandinavian hospitals for a number of years (Mørch and Muller, 1937) In the course of the past 30 years, however it has been abandoned in several clinics being replaced by the Manchester operation (Bierring and Bohn 1957 and others)

Subsequently other methods of abdominal hysteropexy have been advocated Schultz (1948) described a method of fixing the uterus to the sacral promontory whereas Peterson and Arje (1951) have suggested hysteropexy by stitching the uterosacral ligaments behind the uterus and suturing the cardinal ligaments to the anterior surface of the cervix Neither of these methods has achieved much popularity

In the Spalding Richardson operation which is a combined vaginal-abdominal procedure the cervix and fundus are amputated The isthmic area is preserved together with its supporting structures and after excision of the endometrium it is suspended by the round ligaments the Fallopian tubes and the ovarian ligaments This method is said to give good results but it is not

likely to be introduced as a routine procedure since it is fairly extensive and technically complicated

At this Department which has been in the charge of the same gynæcologist since it was established in 1937 the methods of surgical treatment of genital prolapse have not altered The present study comprises a review of a representative series of cases and presents the methods of treatment and the results obtained Several of the methods described above have been u ed and the case material demonstrated what may be accomplished by adapting the treatment to individual conditions

Case Material

The case material comprises all patients operated upon for utero vaginal prolapse during a 7 year period (1948—1954) a total of 443 cases

Surgical treatment was employed when gynæcological examination showed pronounced cystocele rectocele or descent of the cervix down to or out ide the vulva

The mildest cases of prolapse in which the symptoms were caused by pouching of the vaginal wall without an actual cystocele or rectocele and in which the cervix did not reach down to the level of the vulva were treated primarily by pessary In these mild cases urgical treatment was resorted to only if sufficient upport for the pessary could not be obtained from the pelvic floor or if the pessary failed to relieve the symptom

Severe cardio va cular disease or other organic lesions resulting in general debility sometimes contra indicated surgery and such patients were also treated by pes ary

During the period under discussion a total of 166 patients were discharged with a pes ary as definitive treatment most of them because the descent was so slight that operative treatment was not indicated These cases were not included neither were patients who had colporrhaphy performed because of urinary incontinence unless genital descent had been demonstrated at the same time

Clinical Details

The *age distribution* is shown in Table I, 289 patients (65 per cent) were aged 50 years or over at the time of operation, 29 were over 70 the oldest being 79 years. Advanced age *per se* was not a contra-indication to surgery. Only 57 patients were under 40 years of age (the youngest being 25), this is because we have been reluctant to operate on patients of child-bearing age. A similar age distribution has been found in other major Scandinavian series (Danielson, 1957, Svennerud, 1958) although in Anglo American literature the mean age is often somewhat lower (Solomons, 1955, Wood, 1957).

Table I. *Age Distribution (443 Patients)*

Age	20–29	30–39	40–49	50–59	60–69	70–79
No. of patients	6	51	97	157	103	29

Table II lists the patients according to *parity*. Eight were nulliparous, and the largest number of deliveries was 15 (one patient). The majority had borne 2 or 3 children, which is the commonest parity for Danish women. The parity distribution showed no significant difference from that in the general female population of similar age distribution in Denmark. A similar parity distribution was found in the Scandinavian reports mentioned above. These findings confirm the suggestion that parity is not a cause of uterine prolapse.

Table II. *Number of Deliveries prior to Operation (443 Patients)*

No. of Deliveries	No. of Patients	Per Cent
0	8	1.8
1	51	11.5
2	110	24.8
3	97	21.9
4	54	12.2
5	54	12.2
6 or over	69	15.6

In order to elucidate the role of *birth trauma* Table III gives the frequency of complications of delivery among the 435 patients who had given birth to children Infants with a birth weight of 4 000 g and over had been born to 209 patients (48 per cent) 37 women (8 8 per cent of the entire series) had borne infants weighing 5 000 g and over Prolonged labour is defined as a labour lasting more than 24 hours in a primigravida or more than 12 hours in a multigravida It occurred in 72 cases (16 6 per cent) It must be stre sed that the figures listed in T ble III are based chiefly upon data given by the patients themselves and thus should be regarded with some reserve

Table III *Complications of Deli ery (435 Patients)*

Com lications of Delivery	No of Patients	Per Cent
Baby — > 4 000 g	209	48 0
Forceps delivery	34	8 0
Puerperal infection	16	3 7
Prolonged labour	72	16 6
Large perineal lacerations	40	9 2

With regard to the *time of onset in relation to the last delivery* 40 patients reported that the first symptoms had been present prior to the last delivery and 63 that symptoms had developed within the first year of the last delivery In 269 cases the initial symptom was noted one to twenty five years after the last deliv ery with an approximately equal distribution through the years In 63 cases the disease did not begin to manifest itself until more than twenty five years after the last delivery

The *period elapsing from the onset of symptoms in il surgical treatment was instituted* was extremely varied Only 73 were operated upon within the first year 184 came to operation from one to five years after the initial symptom 91 from six to ten years and 95 more than ten years *after* the onset

A total of 187 patients had been using pessaries for varying periods prior to surgical treatment

Thirty (6 9 per cent) had previously had operations for genital prolapse and thus represented recurrences

Seventeen had had supravaginal hysterectomy because of various non malignant diseases prior to the onset of prolapse

Symptoms and Signs

Symptoms before the operation are listed in Table IV Practically all the patients complained of pelvic pressure and the majority had noted that something was protruding outside the vulva On the basis of the case records, it was impossible to decide whether the symptom of backache was due to the prolapse or to causes outside the pelvis

Table IV *Pre-operative Symptoms (443 Patients)*

Symptoms	No of Patients	Per Cent
Pelvic pressure	430	97 1
Protrusion	365	82 4
Backache	196	44 2
Pelvic pain	135	30 5
Stress incontinence	173	39 1
Recurrent cystitis	46	10 4
Frequency of micturition	211	47 6
Other disturbances of micturition	133	30 0
Disturbances of defecation	38	8 6
Vaginal discharge	149	33 6

The *signs* of prolapse were assessed with the patient in the dorsal lithotomy position The degree of vaginal descent stated in Table V refers to the findings when the patient was straining The terms cystocele and rectocele refer to cases in which the vaginal wall descended to or beyond the vulva Descent of the uterus was assessed by pulling the cervix down with a tenaculum while the patient was straining Sixty six patients had complete prolapse that is procidentia Digital examination disclosed retroflexion of the uterus in 105 cases

It has been suggested that uterine prolapse is but one main

Table V. *Pre-operative Signs (443 Patients)*

Descent of Vagina	Cervix Above Vulva	Cervix Reaching Vulva	Cervix Outside Vulva	Total
Cystocele and rectocele	64	44	91	199
Cystocele (without rectocele)	53	37	57	147
Rectocele (without cystocele)	36	9	13	58
Neither cystocele nor rectocele	3	2	34	39
	156	92	195	443

festation of a generalised mesenchymal weakness. In support of this it was observed that 118 of our patients (26.6 per cent) had varicose veins, 181 (40.9 per cent) had flatfoot, and 43 (9.8 per cent) gave a history of operation for hernia. The majority of the patients were also questioned regarding the occurrence of prolapse, hernia, varicose veins and flatfoot among their immediate family. The data indicate the possibility of an inherited ætiological factor, but no firm conclusions can be drawn as a control series is not available.

Types of Operation

Table VI lists the types of operation. The usual procedure was *anterior colporrhaphy and colpoperineorrhaphy*, supplemented by ventrofixation of the uterus in cases where uterine descent predominated, where the uterus was retroflexed, or where follow-up examination after vaginal operation showed a tendency to recurrence.

If pre-operative examination showed only cystocele and the pelvic floor was sufficiently strong, the operation was restricted to *anterior colporrhaphy*. Conversely, if examination revealed only rectocele, *colpoperineorrhaphy* alone was performed. In some cases these operations were supplemented by ventrofixation according to the criteria mentioned above.

The *Manchester operation* (45 cases) was used for treatment of procidentia in patients under 60 years of age, especially in cases with hypertrophy or elongation of the cervix. Thirty-nine of these patients had colpoperineorrhaphy performed at the same

Table VI. *Type of Operation (443 Patients)*

Type of Operation	No. of Patients
Anterior colporrhaphy and colpoperineorrhaphy	127
Ditto with ventrofixation	109
Anterior colporrhaphy	20
Ditto with ventrofixation	29
Colpoperineorrhaphy	43
Ditto with ventrofixation	15
Manchester operation	35
Ditto with ventrofixation	10
Le Fort Neugebauer operation	53
Other procedures	2
	443

time and, as shown in Table VI, the Manchester operation was supplemented by ventrofixation in 10 cases.

Ventrofixation was carried out in a total of 165 cases. In 17 colporrhaphy and ventrofixation were performed at the same time, in 91 cases the abdominal operation was done ten to fourteen days after the vaginal procedure, and in 57 cases the patient was discharged after the vaginal operation and later re-admitted for ventrofixation.

In cases of procidentia affecting patients over 60 years of age the standard method was *median colpocleisis by the Le Fort Neugebauer method*, usually combined with colpoperineorrhaphy. The Le Fort Neugebauer operation was also used in patients under 60 years of age with complete prolapse, provided that the loss of the ability to have sexual intercourse was not important. Thus, 13 out of the 53 patients listed in Table VI were between 50 and 60 years of age.

One patient had vesico-vaginal interposition of the uterus by the Schauta-Wertheim method, and one had amputation of the cervix as well as ventrofixation, but without colporrhaphy.

In 13 cases in which the genital prolapse co-existed with another gynaecological disorder (in most cases fibromyomata or functional bleeding disturbances), the vaginal plastic repair was supplemented by abdominal subtotal hysterectomy.

Surgical Technique

Anterior colporrhaphy as well as colpoperineorrhaphy was carried out according to conventional methods separating the bladder and the rectum from the vaginal mucosa without dissecting the vesico vaginal or recto-vaginal fascia free and infolding the wall with purse string or interrupted sutures In 71 cases the anterior colporrhaphy was supplemented by Kelly sutures Colpoperineorrhaphy included exposure of the levator muscles which were united with 2—4 interrupted sutures The amount of mucosa excised was limited so that suturing could be accomplished with exact approximation of the wound edges and without tension Stress was laid on complete hæmostasis before suturing

In the Manchester method 2—4 cm of the cervix was removed the cardinal ligaments were joined anterior to the uterus, and the cervix re formed by the Sturmdorf method Regarding the technique of colpocleisis the interested reader is referred to previous reports from this Department (Kuhnel 1942 1951)

The suture material was iodized catgut of fine calibre but the levator and Sturmdorf procedures were done with strong chromic catgut

Ventrofixation was carried out by the Kocher method using silk sutures In order to reduce the risk of post-operative intestinal obstruction the utero vesical pouch was always closed with seroserous sutures When ventrofixation was performed in women of child bearing age sterilization by the Madlener method was carried out after obtaining the patient s consent

The operations were carried out by the consultant or the senior registrar (3 different persons during the period concerned) and in only a very few cases by the junior registrar

Anæsthesia

In 236 of the vaginal procedures low spinal anæsthesia was employed using a 0 25 per cent hyperbaric solution of *nupercaine* hydrochloride In nearly all cases this gave adequate anæsthesia both in regard to area and duration Only a few mostly apprehensive and nervous patients required a supplement of light general

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this is defined as suppurative inflammation in the area of the operation, entirely superficial necrosis of the wound edges is not included. Pyrexia recorded in 40 cases refers to elevation of temperature above 38° C for more than 48 hours. During the first four post-operative days the temperature was taken in the axilla, thereafter in the rectum.

Table VII *Post-operative Complications in 106 out of 443 Patients*

Post-operative Complications	No. of Patients	Per Cent	Deaths
Wound infection	21	4.7	1
Urinary infection	56	12.6	0
Pyrexia	40	9.0	0
Phlebitis	9	2.0	0
Pulmonary embolism	8	1.8	2
Pneumonia	7	1.6	0
Post-operative bleeding	2	0.5	0

* One patient died from an unknown cause.

On the day of operation one patient had profuse hæmorrhage from the vaginal wound, and in another case severe bleeding started from the vaginal operative field on the 7th day. Both were treated by packing the vagina. There were no other instances of hæmorrhage requiring treatment, or of major hæmatomata in the operative field, but in a few cases bruising was observed around the perineal wound.

As apparent from the first history given below, vesico-vaginal and recto-vaginal fistulæ occurred in one case following abscess formation in the operative field. Apart from this single case no fistulæ were found either during the stay in hospital or at the follow-up examination.

Four patients (0.9 per cent) died eight to forty-seven days after the operation, two of pulmonary embolism, one of infection in the wound, and one of an unknown cause. The histories of these 4 cases are briefly reported below.

anaesthesia (nitrous oxide-oxygen or intravenous pethidine) In some cases spinal anaesthesia led to moderate hypotension shortly after the induction Occasionally the blood pressure had to be raised by intramuscular or intravenous ephedrine, but there were no alarming complications, such as incontrollable hypotension or shock During the post-operative course, there were no serious complications attributable to the anaesthesia, and in particular no meningeal reactions or persistent headache At follow up one patient complained of occasional pain at the site of the lumbar puncture but no other late complications were encountered

In aged and debilitated patients we used local infiltration anaesthesia

General anaesthesia was used for all abdominal operations For vaginal procedures, it was used only in special circumstances for example if a patient showed signs of cerebro spinal disease deformity of the lumbar spine or had a marked aversion to spinal anaesthesia

Post-operative Management

After the operation the patients were confined to bed for eight to ten days An in dwelling catheter was not used but catheterization was carried out twice to three times daily until spontaneous emptying of the bladder had been completely restored

Antibiotics and chemotherapy were used only if there was a special indication They were never used as a routine prophylactic measure Treatment with oestrogens before and after the operation to promote wound healing (Svennerud 1958) was not used

The stay in the Department after vaginal operations averaged 13 3 days ranging from eight to fifty seven days A coincident abdominal operation did not prolong the stay Patients who had vaginal and abdominal operations in two stages during the same admission remained in hospital for an average of 23 2 days with a range of sixteen to forty one days

Post-operative Complications

One hundred and six patients had a total of 143 complications as shown in Table VII Wound infection occurred in 21 cases

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The stay in the Department after vaginal operations averaged 13.3 days, ranging from eight to fifty-seven days. A coincident abdominal operation did not prolong the stay. Patients who had vaginal and abdominal operations in two stages during the same admission remained in hospital for an average of 25.[illegible] days, with a range of sixteen to forty-one days.

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Reports of Cases

Case 1 (Case rec 509/48) The patient aged 59 years had complete prolapse with erosion of the most prominent part of the mucous membrane After the mucosal lesion had healed, anterior colporrhaphy with amputation of the cervix was carried out under local infiltration anaesthesia Post-operatively, she ran a low grade temperature up to 38° C, for a few days but she was fit for discharge eleven days after the operation Four days later she was re admitted in great pain with a high temperature and a gangrenous wound in the vaginal vault The gangrene spread perforating the bladder and rectum and the patient deteriorated dying forty seven days after the operation Autopsy revealed subperitoneal cellulitis and an abscess in the true pelvis with perforation of the rectum and bladder by the abscess

Case 2 (Case rec 715/48) The patient was 38 years old Examination on admission showed a subtotal prolapse She was obese her height being 163 cm and her weight 90 kg Under general anaesthesia, Manchester operation combined with colpoperineorrhaphy was performed From the fifth post operative day there were signs of deep phlebitis of the left leg The patient died suddenly eight days after the operation Autopsy revealed embolism in the pulmonary artery and right cardiac ventricle

Case 3 (Case rec 2162/52) The patient was 67 years old Pre-operatively there was a large cystocele and the vaginal cervix could be brought 1 cm outside the vulva Anterior colporrhaphy was performed under spinal anaesthesia From the fifth to eighteenth post operative days there was some elevation of temperature, but on the twentieth day the patient was discharged to her home in good health For the next ten days she felt well but then developed chest pain and fever After short lasting improvement death occurred suddenly on the thirty ninth post operative day An autopsy was not performed

Case 4 (Case rec 1938/53) The patient aged 72 years had twenty two years previously had an operation for a stone in the right renal pelvis On this occasion she was admitted because of procidentia Stones were found in the bladder and the patient was transferred to a surgical department where the stones were removed by way of the urethra After her return to this Department median colpocleisis by the Le Fort Neugebauer method and colpoperineorrhaphy were performed under spinal anaesthesia The immediate post operative course was uneventful and at the end of twelve days the patient was discharged for convalescence in a private nursing home Four days later, that is sixteen days after the operation she died of pulmonary embolism No autopsy was performed

Follow up

The follow up examinations were carried out during the period December 1958 to May 1959 Out of the 443 patients four died

during the immediate post-operative period. During the follow up period another 34 patients died. In these cases the cause of death is not known.

Out of the remaining 405 (Table VIII) 372 have been interrogated and examined (368 by the authors and 4 elsewhere). The follow up period averaged 7.7 years, ranging from four to eleven years. A further 20 patients answered questionnaires regarding their condition. They were not examined either because they could not attend by reason of disease or old age or because they refused to have a gynaecological examination. In 13 instances it was impossible to contact the patients as they had moved to other parts of the country or they failed to reply despite repeated enquiries (6 cases).

Table VIII. *Follow-up of 405 Surviving Patients*

Follow-up	No. of Patients	Per Cent
No. of patients examined	372	91.9
No. of patients who answered questionnaire	20	4.9
No. of untraceable patients	13	3.2
Total	405	100.0

The *therapeutic results* (Table IX) were evaluated on the basis of the *objective findings* using the same diagnostic criteria as described for the pre-operative study. The results were classified as follows:

Good — No recurrence of signs at the time of the follow up examination.

Improved — Slight pouching of the anterior or posterior vaginal wall but without descent to the level of the vulva.

Recurrence — There was a return to the pre-operative state.

The *symptoms reported by the patients* at the time of follow up accorded largely with the objective assessment. 320 (86 per cent) said the result was good; 34 (9 per cent) found that their symptoms were improved but were not entirely relieved and 18 (5

Table IX. *Results of Operation in 372 Re-examined Patients*

Type of Operation	Good	Improved	Recurrence	Total
Anterior colporrhaphy and colpoperineorrhaphy	90	16	–	108
Ditto with ventrofixation	82	14	2	98
Anterior colporrhaphy	11	3	3	17
Ditto, with ventrofixation	19	4	0	23
Colpoperineorrhaphy	33	1	1	35
Ditto with ventrofixation	13	1	0	14
Manchester operation	29	0	1	30
Ditto, with ventrofixation	6	2	2	10
Le Fort Neugebauer operation	30	4	1	35
Other procedures	1	0	1	2
	314 (84.4 %)	45 (12.1 %)	13 (3.5 %)	372 (100 %)

per cent) did not think the operation had improved their condition.

The *recurrences* are listed in Table X *according to type of operation*. It is evident from this Table that all age groups and types of operation are represented. The onset of the recurrence is considered to be the time when symptoms were noticed. Five recurrences occurred within the first year, 6 between the first and fifth year after the operation and 1 seven years after the operation. In 1 case the recurrence had given rise to no symptoms at all, so the time of its onset cannot be stated.

In 6 cases the recurring symptoms were so slight that no treatment was required. Five patients had a further operation and 2 were *wearing pessaries at the time of follow up*.

In the follow up series there were 30 cases of cystocele treated by anterior colporrhaphy alone. Ten of these patients had subsequently developed a rectocele. This indicates that colpoperineorrhaphy should be performed in almost every case and even in those without demonstrable rectocele. This view is contested by Jeffcoate (1955) who considers that routine colpoperineorrhaphy is not justified because of the increased risk of dyspareunia due to narrowing of the introitus.

Similarly, among 49 patients treated for rectocele by colpo

Table X *Recurrences (13 Patients)*

Type of Operation	Age at Operation	Recurrence Years after Operation	Type of Recurrence	Treatment of Recurrence
Anterior colporrhaphy and colpoperineorrhaphy	31	2 years	Cervix outside vulva enterocele	No treatment
Ditto with ventrofixation	35	5 years	Cervix outside vulva	Re-operation
Ditto with ventrofixation	68	less than 1 year	Large cystocele	No treatment
Ditto with abdominal subtotal hysterectomy	50	2 years	Small cystocele cervix outside vulva	No treatment
Anterior colporrhaphy	47	No symptoms	Small cystocele	No treatment
Ditto	37	7 years	Large cystocele	Pessary
Ditto	54	4 years	Large rectocele	No treatment
Colpoperineorrhaphy	63	Less than 1 year	Large rectocele enterocoele	No treatment
Manchester operation with ventrofixation	38	1 year	Small cystocele enterocoele	Re-operation
Ditto	40	3 years	Large rectocele enterocele	Re-operation
Manchester operation with abdominal subtotal hysterectomy	49	Less than 1 year	Small cystocele *cervix outside vulva*	No treatment
Le Fort — Neugebauer operation	61	Less than 1 year	Procidentia	Re-operation
Interposition of uterus by the Schauta-Wertheim method	44	5 years	Small cystocele	Re-operation

perineorrhaphy with or without ventrofixation follow up examination revealed cystocele which had *not* been present *before the* operation Table XI shows that cystocele developed in about half the patients who did not have ventrofixation as compared with less than one third of the patients treated by ventrofixation The numbers are small and do not warrant any firm conclusions but they do indicate that ventrofixation contributes to preventing descent of the anterior wall

Table XI *Follow-up Findings Concerning Cystocele in 49 Patients Operated upon for Rectocele*

Type of Operation	Total No. of Patients	Patients with Cystocele	Patients without Cystocele
Colpoperineorrhaphy	35	17	18
Ditto with ventrofixation	14	3	11
	49	20	29

Enterocele Thirty-four (9.8 per cent) of the patients showed enterocele at follow-up, but its presence is not interpreted as a recurrence. Only 8 had symptoms, in the form of a sensation of pressure, protrusion, or dyspareunia. In the remaining cases the patients were free of symptoms or else their complaints could be related to other forms of prolapse. Four of the patients with actual recurrence also had a coincident enterocele.

In a follow-up of 219 patients who had undergone various types of vaginal operations Bach-Nielsen and Stakemann (1957) found enterocele in 2. In both cases it was asymptomatic. Gordon and Gordon (1957) demonstrated enterocele in 4 out of 108 patients who had undergone a Manchester operation. Among Danielson's (1957) 189 patients who were asymptomatic following vaginal operation 3 were found to have enterocele, but the frequency of enterocele among patients with post-operative symptoms is not stated. In Bierring and Rasmussen's (1947) series of 89 patients treated by ventrofixation 9 had enterocele.

Table XII gives the cases of enterocele in relation to the type of operation. Although the values in the two groups are not directly comparable, as the indications for operation differed

Table XII *Follow-up Findings Concerning Enterocele (347 Patients)*

Type of Operation	No. of Patients	Enterocele	Per Cent
Colporrhaphy	[illegible]4	6	[illegible]
Ditto, with ventrofixation	14[illegible]	[illegible]8	[illegible]7
	37[illegible]	[illegible]4	9.[illegible]

they do indicate that ventrofixation favours the development of enterocele

Ventral hernia was demonstrated in 2 cases (1 4 per cent) among the 148 treated by ventrofixation In both cases it consisted of a reducible incisional hernia not larger than a plum, situated just above the fixed uterus In general the frequency of hernia following ventrofixation is reported to be 7—10 per cent (Morch and Müller 1937 Bierring and Rasmussen 1947)

Dyspareunia Out of 337 patients (the total follow up series less 35 treated by the Le Fort Neugebauer operation) 64 (18 9 per cent) reported that they were suffering from dyspareunia Viberg (1955) has reported such difficulties in 32 (31 1 per cent) of 103 cases 63 patients who reported that they had not attempted intercourse having been excluded Danielson (1957) had 47 case (10 per cent) of dyspareunia among 466 patients questioned after the operation and in Svennerud s series (1958) 55 (18 5 per cent) out of 302 patients reported that coitus had not been possible after the operation

Stress incontinence Out of the 372 patients included in the follow up study 150 (40 per cent) had suffered from incontinence prior to the operation At follow up the symptom had disappeared in 107 whereas 43 patients still suffered from stress incontinence In another 16 patients stress incontinence had allegedly developed after the operation Thus a total of 59 patients (15 1 per cent) had stress incontinence after the operation

Kelly sutures combined with anterior colporrhaphy did not appear to have any convincing effect upon stress incontinence Only 33 out of 56 patients so treated were symptom free after the operation whereas stress incontinence was cured in 74 out of 94 patients who had surgical correction of the prolapse without Kelly suture

Other forms of urinary symptoms (frequency of micturition recurrent cystitis sensation of residual urine) were observed in 68 cases This is a fairly high percentage but is not surprising in view of the common occurrence of urinary complaints among female patients in the age group concerned

None of the patients included in the follow up had been pregnant after the operation.

There was no case of *genital malignancy* among the patients in the follow-up group.

In addition to the patients included in the follow up 20 *patients answered questions concerning their condition.* Eighteen reported that the result of the operation was entirely satisfactory, whereas 2 stated that the treatment had not relieved the symptoms, but the presumed recurrence had not been treated.

Discussion

The present series of cases was in no way selected, as it comprises all patients with genital prolapse treated surgically at the hospital during the period concerned.

A number of different types of operation were used and the treatment was adapted according to the anatomical changes, age, and general condition of each individual patient. The results therefore do not permit an evaluation of the relative efficacy of the operative methods.

Evaluation of the therapeutic result was based on the objective findings at the follow-up examination, as it was considered that the patient's own assessment of her condition was unreliable. At follow up one frequently saw patients who reported complete freedom from symptoms although a moderate descent was easily demonstrable. Conversely, patients of the age group studied often have a number of non specific symptoms (backache, a feeling of distension, constipation, fatigue) which they ascribe to the genital disease although there is no demonstrable organic basis; this would affect the subjective estimate of the therapeutic result. However, there was no major disagreement in the overall evaluation of operative treatment, the results being interpreted as good according to the objective findings in 84.4 per cent of the cases and according to the patients' own estimate in 86 per cent.

Operative mortality was low (0.9 per cent) as is to be expected in such a condition. In a series including a large number of aged and debilitated persons it can hardly be lowered any further. In all major series the mortality rate has been about 1 per cent. Thus

Phaneuf (1954) reported 1 3 per cent Svennerud (1958) 1 3 per cent Danielson (1957) 0 6 per cent and Bach Nielsen and Stakemann (1957) 0 4 per cent Our use of a long period of post operative bed rest (eight to ten days) resulted in very few cases of post operative bleeding yet the incidences of thrombo embolic complications (1 8 per cent) and respiratory infections (1 6 per cent) were low

The 13 recurrences (3 5 per cent) are fairly widely distributed through the different operative methods In similar series Danielson (1957) and Svennerud (1958) found 7 3 per cent and 9 4 per cent of cases recurred respectively In general a recurrence rate of less than 10 per cent should be obtainable in non selected series using the types of operation available to day

A feature of the present case material is the common practice of anchoring the uterus to the anterior abdominal wall as a supplement to colporrhaphy It is believed that ventrofixation reduced the frequency of recurrences in the patients with a major degree of prolapse and counteracted the development of cystocele in patients who did not have anterior wall descent prior to the operation

Enterocele was demonstrated in 9 per cent of all the patients included in the follow up being particularly common among patients who had had ventrofixation The values found in previous studies combined with the present material show that the frequency of enterocele is less than 4 per cent following vaginal operations but that it is considerably higher following ventrofixation *(10—20 per cent)* *This* is due to the fact that the entire intra abdominal pressure is exerted on a weak site when the uterus is drawn forward The operative risk was not increased by the ventrofixation procedure and the *number* of incisional hernias (2 cases) was so low that this cannot be said to encumber the method

At follow up 64 patients reported dyspareunia Although this is a fairly high proportion it is not greater than is usual after operations *for* uterine prolapse The series does not permit a further analysis of this symptom partly because it is not known how many patients had sexual difficulties prior to the operation and partly because the term dyspareunia may cover a wide range

of conditions, from commonplace post-operative anatomical structures to pure neuroses without any organic basis.

Urinary incontinence, especially in the form of stress incontinence, is common among elderly women, even in the absence of prolapse. It was present in 15.9 per cent of the patients at follow-up. This cannot be compared with previous series, since the reported frequency is so varied that it is obvious that the definition of this symptom must differ. For instance, it is stated by Solomons (1955) that in a series of 62 patients none had stress incontinence, either before or after the operation, whereas Bach-Nielsen and Stakemann (1957) reported that among 68 patients 25 had incontinence before the operation and 29 at follow-up.

SUMMARY

During a 7 year period (1948—1954) 443 operations for genital prolapse were performed at the Gynaecological Department of the Odense County and City Hospital, Odense, Denmark.

The type of operation depended upon the degree of prolapse and the patient's age. The commonest procedure was simple colporrhaphy (343 cases) supplemented in almost half the cases (153) with anchorage of the uterus to the anterior abdominal wall by Kocher's method. Subtotal or total prolapse in younger patients was treated by the Manchester procedure (45 cases) combined in most cases with colpoperineorrhaphy and in some cases with ventrofixation. Patients over 60 years of age with procidentia were treated by median colpocleisis by the Le Fort Neugebauer method (53 cases).

The vaginal procedures were carried out under low spinal anaesthesia in more than half the cases (238). This gave satisfactory anaesthesia and there was a notable absence of primary or secondary complications.

Four patients (0.9 per cent) died during the post-operative period, two of them from pulmonary embolism, one from infection in the operative field and one from unknown cause. Thirty four died during the follow up period.

Out of 405 survivors 372 (91.8 per cent) attended for follow up examination at the end of a period of from four to eleven years (average 7.7 years) and an additional 20 answered a questionnaire. No data are available for 13 cases. In 314 cases (84.4 per cent) the therapeutic result was good. In 45 patients (12.1 per cent) the condition had improved without being entirely satisfactory although it was not sufficiently unsatisfactory to justify a further operation. Thirteen patients (3.5 per cent) had a recurrence at intervals up to seven years after the operation.

In general each of the operative methods gave good results providing their limitations were recognized. Because of the selection of cases based on the clinical findings it is not possible in the present series to compare the relative values of the different methods.

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TWO CASES OF CERVICAL PREGNANCY

BY

M THOMSEN AND F JOHANSEN

> The great majority of certified obstetricians will never see a cervical pregnancy The minority who do happen to encounter this complication will probably wish that they had not (Baptisti 1953)

Cervical pregnancy occurs when the ovum is implanted and develops in the mucous membrane of the cervical canal Schneider (1946) has termed it distal ectopic pregnancy and proposes the following classification (1) 'pure cervical pregnancy (2) isthmico-cervical pregnancy, and (3) endometrio-isthmico cervical pregnancy In group 1 the placenta is localised to the cervix and the internal os is closed, whereas in group 2 it is assumed that nidation occurs in the cervix and that the placenta secondarily spreads to the isthmic area or vice versa Group 3 includes most of the cases which were earlier described in the literature as cases of cervical pregnancy and which have been subdivided by Zangemeister and Schilling (1922) into a) Placenta cervicalis dissecans b) Placenta partim cervicalis and c) Placenta totaliter sive præcipue cervicalis Ingerslev (1956) notes that purely cervical pregnancy is seen from an anatomical point of view intra uterine, although functionally it is extra-uterine Whereas early publications included all three of Schnei-

der's groups, recent writers include only the first two groups under the title cervical pregnancy' The symptoms in these two groups are nearly identical, and very different from those in the other varieties where *only a part of the placenta is attached to* the cervix

Cervical pregnancy is extremely rare, Paalman and McElin (1959) found only 5 cases in a series of 47,974 pregnancies admitted to two American hospitals during the years 1945 to 1955, an incidence of 0 01 per cent

Two cases of isthmico cervical pregnancy are reported below

Report of Cases

Case 1 St Maria Hospital, Vejle, Gyn Obst Dept
Case history No 348/59

A 43 year-old woman, para 3 gravida 5

Menstrual cycle 4/21 days

In 1936 she had a forceps delivery at term in 1938 and 1943 there were normal deliveries and in 1948 she had a therapeutic abortion

The last menstrual period late in January 1959 was less heavy than usual and followed by one day of spotting in the middle of February Increasing vaginal hæmorrhage occurred for three days before admission when pain developed over the lower part of the abdomen

She was admitted on 28th March 1959, with the diagnosis of acute endometritis and thrombophlebitis of the left leg

On admission the patient s general condition was good Blood pressure 140/80 temperature 38 0°C, and pulse 100 Varicose veins showing superficial phlebitis were present on the left leg There was considerable tender ness over *both* inguinal ligaments Vaginal examination *revealed profuse* secretion in the vagina, the cervix was distended and the anterior lip cyanotic The external os was dilated and through it it was possible to palpate a tense amniotic sac The state of the uterus corresponded to a 2–3 months pregnancy There were no palpable masses lateral to the uterus

As spontaneous abortion had not occurred by the third day the patient was re-examined no changes were disclosed Terramycin was given prophylactically and a general anæsthetic administered By means of a blunt curette a nearly 10 cm long macerated fœtus and a large amount *of placental tissue were evacuated from the uterus Difficulty* was experienced in emptying the cavity and there was profuse hæmorrhage The total volume of tissue and blood was 1 600 ml Methylergometrine and oxytocin intra venously appeared to produce hæmostasis Dextran 6 per cent was given A little less than half an hour after the operation and before blood transfusion had been commenced, the patient had a series of rigors her temperature



Fig 1 Opened uterus from Case 1

rose to 39 7 C and the profuse vaginal bleeding recommenced She was re-examined and the source of the severe hæmorrhage was found to be the external os The uterus was atonic and elongated and the cavity was 30 cm long Uterine tamponade was performed followed by abdominal subtotal hysterectomy as an emergency procedure During and after operation the patient received 2 000 ml whole blood 1 000 ml Dextran 6 per cent, and 6 g human fibrinogen the shock being thereby corrected

Cervical pregnancy was first suspected when the uterus was opened (Fig 1) and it was noted that the placental site was localised to the internal os and the dilated thin walled cervix, whereas the upper part of the uterine cavity was smooth

Histological examination (J Vesterdal Jørgensen) The opened fixed uterus measured 11 cm the cavity 8 cm the wall being 3 cm, thick at the fundus ½ cm in the cervical region The upper 3 cm. of the cavity were smooth the site of placental implantation occupying the lower 5 cm It was impossible to localise the internal os Microscopy failed to disclose cervical glands or mucous membrane but at the lowermost end of the cervix there were fragments of villi and trophoblastic cells implanted upon the musculature indicating that there must have been placenta accreta Corresponding to the



Fig 2 Section from cervix S te of in plantation with large cells (transformed smooth muscle cells?)

placental s te was a zone of necros s witl out inflammation In an area 3 5 mm wide under tl e necrotic zone tl ere were degenerate smooth muscle cells togetl er with a pecul ar type of atrophy involving a large amount of smooth muscle tissu wl ich appeared to have been dissolved In the same area (F g 2) tl ere were also numerous large cells whose appearance resem bled that encountered in pronounced syncytial endometr tis The major ty of the cells seemed to have been deri ed from smooth muscle altl ough tl e poss b lity tl at some of them n ght have der ved from the tropl oblast could not be excluded The large cells were ma nly concentrated n tl e walls of the blood vessels i i most instances tl ey were present both in the walls fac ng tl e placental s te and n tl ose facing away from it but n a few vessels the cells were present in large n mbers only in tl e walls facing away from tl e cav ty In a few places t was poss ble to see tl at tl e large cells wh ch were somewhat elongated and lay w th tl eir axes parallel to each other had been der ved d rectly from smooth muscle cells Tl e



F g 3 Section from fundus uteri Cells with slight s gns of pregnancy

major ty of the cells were med um s zed sl ghtly rounded and were taken to be smooth muscle cells exhib ting decidual response They showed a marked tendency to occur in cha ns perhaps correspond ng to the lymph vessels The decidual response was restricted to a surprisingly sharply defined area and there were no signs of decidual response in the deeper layers of the muscular s mucosae where there was however sl ght muscular hypertrophy Sect ons from the upper part of the cavity (F g 3) showed that the stroma consisted of small cells w thout decidual reaction The glands were tubular and the cells e ther proliferating or a little larger A few glands could be seen to ha e secreted and conta ned nuclei of the Ar as type

M roscop c d agnos s Gra ditas reg on s cervicis uteri placenta accreta pecul ar transformation of smooth muscle

The post-operati e course was uncompl cated On vag nal examination at tl e pat ent s discharge t was found that there were shell shaped remains of the anterior and posterior cerv cal lips the ovaries were walnut sized and there were no abnormal masses in the pelvis.

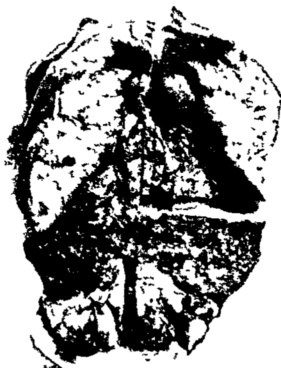


Fig 4 Sectioned uterus from Case 2

Case 2 The State Hospital, Sonderborg, Gyn Obst Dept.
Case history No 1,041/59

A 38 year old para 2, gravida 4 was admitted in the third month of pregnancy with a diagnosis of missed abortion and with a history of spotting for four weeks

In 1954, the patient had a therapeutic abortion for psychogenic psychosis with mental depression primary evacuation in the 9th week foetus, 5 cm

In 1955 tubal insufflation for secondary sterility was performed

In 1956, classical Cæsarean section was carried out for total placenta prævia and a living male weighing 2 650 g was delivered

In 1958 she had a normal delivery though with protracted labour Three weeks later uterine curettage was performed for post partum metrorrhagia A little old placental tissue was removed and it was noted that the cervical canal was rather wide

On admission the state of the uterus was found to correspond to an 11 week pregnancy and on vaginal examination the external os was seen to be dilated and to contain a bluish mucous membrane which was taken to



F g 5 Section from cervix Cystic dilated cervical gland and deeper lying trophoblastic cells

be he amniotic sac The uterine e acuation was therefore commenced. First here was a rush of amniotic flu d Using ovum forceps some placental t ssue was removed, but no fœtal parts were found. It was striking that the mplantat on site was far down in the cervix, and that little could be removed from the fundus. After the ca ity had been scraped clean there was br sk hæmorrhage but the uterus contracted satisfactorily After the administration of Methylergometrine the hæmorrhage subs ded to such an extent that the patient was returned to the ward and g ven Dextran, 6 per cent, and 500 ml whole blood As the hæmorrhage had again become brisk and was unresponsi e to Methylergometr ne the patient was re-examined six hours later The ag na was found to contain a large amount of coagulated blood he external os was d lated with blood clots Re-evacuation was performed but only a small amount of tissue and large amounts of clotted blood were remo ed The coagulation and bleeding times were normal Dextran 6 per



Fig 4 Sectioned uterus from Case 2

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Case history No 1 041/59

A 38 year-old para 2, gravida 4, was admitted in the third month of pregnancy with a diagnosis of missed abortion and with a history of spotting for four weeks

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Rubin proposed that true cervical pregnancy should satisfy the following criteria

(1) There must be cervical glands opposite the placental attachment,
(2) the attachment of the placenta to the cervix must be intimate,
(3) the whole or a portion of the placenta must be situated either below the entrance of the uterine vessels or below the peritoneal reflection on the anterior and posterior surfaces of the uterus
(4) fœtal elements must not be present in the corpus uteri

Schneider (1946) considered that in primary cervical pregnancy the site of implantation ought not to exceed or should only just reach the transition between cervix and isthmus Pregnancies of more than 12 weeks will never fulfill these criteria, as they will overlap the boundaries of the cervix due to their size Schneider repeated this condition in 1957, but added that cervical pregnancies which cannot be classified as primary because they have exceeded the cervico-isthmic boundary are more important from a clinical point of view than are the purely cervical pregnancies as the former are responsible for the most severe hæmorrhage

In 1959 Paalman and McElin suggested the following clinical signs

(1) Uterine bleeding after amenorrhœa and without cramping pain
(2) a softened and disproportionally enlarged cervix equal to, or larger than the corporeal portion of the uterus An hour glass shaped uterus
(3) products of conception entirely confined within and firmly attached to the endocervix
(4) a snug internal os
(5) a partially open external os

The figures given by different authors for the number of previously published cases of cervical pregnancy vary according to the criteria they have adopted thus Schneider (1957) mentions 17 cases whereas Baricalla (1957) states that there

cent, and 500 ml whole blood were again given As the hæmorrhage continued to be brisk, cervical pregnancy was suspected The hæmorrhage, however, ceased after packing, and as the patient responded well to treatment for impending shock, hysterectomy was postponed When the hæmorrhage recommenced it became essential to perform total hysterectomy On opening the peritoneum it was noted that the front of the cervix was thin and bluish The uterus was removed in the normal manner There were no signs of perforation During operation the patient received Dextran, 6 per cent, and a total of 2,000 ml whole blood She responded well and the post operative course was uncomplicated Upon discharge, 14 days later, the vaginal wound had healed, the hæmoglobin was 87 per cent and the sedimentation rate 6 mm

Macroscopic examination of the uterus (Fig 4) disclosed that the upper two thirds of the cervical canal were distended and thin walled, in some places being nearly paper thin, bluish, and transparent

Histological examination (J Vesterdal Jorgensen) Due to the two curettages, little or no mucous membrane was seen in the preparations There was an almost walnut sized submucous fibroid in the fundus, and near to this a small part of the endometrial pars basalis had been preserved This mucous membrane showed no signs of pregnancy reaction, having slim tubular glands neither were there signs of decidual change in the surrounding stroma Sections of the cervical region showed a site of implantation, with a necrotic, blood infiltrated surface The tissue was congested with blood vessels, in the walls and vicinity of which there was typical decidua This was particularly evident around the vein walls Beneath this area, in which two masses of trophoblast were the only remains of the placenta there were characteristic cervical glands some of which were dilated and cystic (Fig 5) The myometrium in general was only slightly hypertrophic

Microscopic diagnosis Status post graviditatem regionis cervicis uteri

Historical review The first case of cervical pregnancy seems to have been reported in 1817 by Sir Everard Home, who found an early ovum in the cervical canal during a post mortem examination In 1860 Rokitansky reported two cases and since then the number of reported cases has rapidly increased, especially during the last few years Two cases have been previously reported from Scandinavia (Meyer 1929, Jacobsen, 1949) Critical reviews of the literature in an attempt to define cervical pregnancy more accurately have been published by Rubin (1911) Concetti (1940), Studdiford (1945) Bowles (1945) Schneider (1946, 1957), Baptisti (1953) and Paalman and McElin (1959)

Pathogenesis The cervical mucous membrane is not affected by normal pregnancy, but in cervical pregnancy one finds alterations resembling those in the tube during tubal pregnancy The trophoblast penetrates the mucous membrane and as there is only slight and often patchy decidua in the cervical canal, the trophoblastic invasion is not checked as much as it would normally be within the corporeal cavity The trophoblast penetrates the cervical wall, which becomes œdematous and richly vascularised In its development the trophoblast is especially apt to follow the blood vessels and in many cases may reach out under the serosa

This rapid invasive development may be compared to a malignant process Blood vessels are often eroded, leading to subovular hæmorrhage and early abortion Such early abortions often take place without the patient or physician noticing them as prior to the 6th week the chorionic villi are but little developed and there is as yet no placenta accreta

Due to the restricted space in the cervix and the trophoblastic activity abortion occurs or the cervical wall may rupture when the cervix can no longer dilate further Rupture may, according to the site of implantation, be into the vagina (Otto, 1934, Gergely 1935), the parametrium (Schweitzer, 1918, Zangemeister and Schilling 1922 Ponfick 1900) or the pouch of Douglas (Rubin 1911, Szenteh 1934) It is characteristic that the ovum is retained in the dilated cervix due to the placenta accreta and can only be removed by surgical intervention

Diagnosis and differential diagnosis Usually the initial symptoms of cervical pregnancy are not alarming After a period of amenorrhœa there is increasing vaginal hæmorrhage usually in the second or third month most frequently painless but sometimes accompanied by slight pain in the lower abdomen and lumbar region In a few cases mild symptoms referable to the urinary tract and dyspareunia have also been observed The initial hæmorrhage will however often occur at such an early stage that pregnancy is not suspected

In typical cases gynæcological examination reveals the portio to be large distended, and hyperæmic and the orifice dilated The cervix is distended tense and cystic corresponding to the dura-

are 70 The present authors have found approximately 80 cases which have been described as cervical pregnancy, in addition to which there are 10–20 known but unpublished cases, so that the total number must be nearly 100

Aetiology Cave (1954) summarizes our knowledge by saying that there have been many philosophical deductions but no facts The predisposing factors may be divided into the maternal and the conceptal

On the basis that the literature contains many cases in which the patient has been an elderly multipara with a history of previous abortions and intra-uterine operations, it has been suggested that distal nidation might be due to atrophy of the endometrium, chronic endometritis or insufficiency of the internal os Purely mechanical factors such as intra uterine myoma, fibromatosis and uterine malformations have also been proposed, as well as alterations in the uterine tone Normally, uterine tone is increased in the body and reduced in the cervix throughout the phase of proliferation, and vice-versa during the phase of secretion (Palmer, 1948) If the conditions of tone from the first phase persist during part of the second phase, this may lead to the ovum being released from the corporeal cavity of the uterus while it is still capable of nidation

Several authors have pointed out that alterations in the relationship between the ovum s speed of passage through the genital tract and its degree of implantation maturity will lead to various types of ectopic pregnancy According to Schneider (1946) the speed of passage is extremely variable

Among the other conceptal factors it has been suggested that cervical pregnancy might be due to retarded development of the blastoderm or of the proteolytic enzymes necessary for implantation, possibly combined with an explosive development in these retarded processes just before the conceptus is discharged from the uterus (Schneider, 1946) Finally, cases have been reported of late fertilisation (four days after ovulation as determined by measurement of the basal temperature) which have led to cervical pregnancy (Ellingson 1950) and nidation on an eroded portio has likewise been said to follow late fertilisation (Keller 1954 Yenen 1955, Jiratko 1955)

Histological demonstration of trophoblastic cells in close relationship to the cervical glands is proof positive that the primary nidation has occurred in the cervix It is frequently also possible to demonstrate degenerative changes with œdema and hæmorrhage in the cervical tissue, and also considerable round cell infiltration At the placental site the mucous membrane consists of high hypertrophic epithelium and large, dilated cervical glands Usually several areas show decidual changes The endometrium within the body of the uterus does not contain any products of gestation and varies in phase from proliferative to decidual, the latter appearing to be the most frequent, corresponding to the sympathetic decidual response occurring in other types of ectopic pregnancy

Treatment The cases reported in the literature have often been treated on the basis of an incorrect original diagnosis Attempts to evacuate the uterus digitally or instrumentally will usually produce violent hæmorrhage, in many cases so severe as to necessitate hysterectomy Several authors report having controlled the bleeding by means of packing, sometimes with fibrin foam, whilst others have obtained hæmostasis by amputating the cervix Utero-tonic agents do not affect the hæmorrhage as the open vessels cannot be closed by contraction of the thin walled, distended cervix which contains but few contractile elements (Danforth 1947) In addition degenerative changes in the elastic fibres of the blood vessel walls have been described (Schneider, 1946) If tamponade provides successful hæmostasis primarily, severe secondary hæmorrhage necessitating hysterectomy may nevertheless occur up to six weeks later (Schneider and Dreizin 1957) Fatal secondary hæmorrhage has also been described (Steinbiss 1928)

At one time it was usual to carry out hysterectomy immediately cervical pregnancy was diagnosed During recent years, however several authors have recommended conservative treatment as improved facilities for blood transfusion permit several attempts at treatment without exposing the patient to serious risk Using conservative methods it has been possible in some cases to avoid hysterectomy and cases have been reported where the patient later gave birth to a normal, living child after a

tion of the pregnancy, and it is sometimes possible to palpate above it the small, hard uterine body, which is of normal size

Differential diagnosis from impending or incomplete abortion may be difficult, as the enlarged cervix may be taken for a normal, pregnant uterus, and the uterine body thought to be a fibroid of the fundus Due to the destructive changes, carcinoma of the cervix or chorionepithelioma have often been suggested as the first diagnosis In one case of *cervical pregnancy hysterosalpingographic* pictures were interpreted as showing a malignant tumour in the cervix, as there was irregular tumour configuration and injection in very dilated vessels (Lambert-Netter, and Belaisch, 1957) Other cases have been confused with early placenta pravia (Bachman, 1955, Crousse, 1933), infected abortion with pericervical infiltration (Jacobsen, 1949), varicose veins of the cervix (Otto, 1934), unilateral pregnancy in a bicornate uterus (Fleischhauer, 1951), torsion of an ovarian cyst (Cummin, 1955) and ruptured tubal pregnancy (Rubin, 1911)

Several of the cases reported as cases of cervical pregnancy must be assumed to be cases of cervical abortion – with which cervical pregnancy is often confused Cervical abortion occurs when the ovum is discharged from the uterine cavity into the cervix and is retained there due to an unyielding external os

The following criteria assist differential diagnosis In cases of cervical abortion the uterine body is larger than normal, the internal os is dilated, the external os is closed, and the placenta lies loose in the cervix and may extend into the cavity of the uterus In cervical pregnancy the uterus is relatively small the internal os is closed or nearly so the external os is soft and slightly dilated, and the placenta is firmly adherent to the wall of the cervix (Duckman and Amico, 1957)

Pathological anatomy and histology Herbut (1953) has given a detailed description of the pathological anatomy of cervical pregnancy The cervix is typically large dilated thin walled and slack, the placental site is rough frayed and bloody, surrounded by pale, smooth mucous membrane and often containing large open vessels Sometimes the area is transformed into a crater like defect due to the invasion of the trophoblast

Histological demonstration of trophoblastic cells in close relationship to the cervical glands is proof positive that the primary nidation has occurred in the cervix It is frequently also possible to demonstrate degenerative changes with œdema and hæmorrhage in the cervical tissue, and also considerable round cell infiltration At the placental site the mucous membrane consists of high hypertrophic epithelium and large, dilated cervical glands Usually several areas show decidual changes The endometrium within the body of the uterus does not contain any products of gestation and varies in phase from proliferative to decidual, the latter appearing to be the most frequent, corresponding to the sympathetic decidual response occurring in other types of ectopic pregnancy

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normal pregnancy (Baptisti, 1953, Burstein, 1954, Paalman, 1959) Several authors consider that conservative treatment is no longer practible after the third month of pregnancy, and early diagnosis is therefore important

Morton (1949) and Burstein (1954) stress that after removal of the ovum one should avoid curettage of the cervical canal, as this procedure is often responsible for the most severe hæmorrhages, due to the opening of large vessels lying deep in the wall of the cervix Instead they recommend the application of primary tamponade, and that the placenta be left *in situ* until it is resorbed as, for example, in cases of abdominal pregnancy Fleischhauer (1951), however, considers that lasting results are only obtained by the total removal of the placenta accreta, as in his patient violent secondary hæmorrhage, due to placental remains, occurred a month after primary hæmostasis

Prognosis The maternal mortality was exceptionally high in the early cases, mainly due to hæmorrhage and sepsis Thus Hofstätter (1911) gives a mortality rate of 66 per cent, Zangemeister and Schilling (1922) one of 43 per cent, Concetti (1940) one of 13 per cent Studdiford s report (1945) states that the mortality in cases of proven cervical pregnancy was 30 per cent, and that in unconfirmed cases 10 per cent, the average mortality for all cases thus being 20 per cent According to Baptisti (1953) the mortality rate in cases published between 1945 and 1953 was only 6 per cent, but Studdiford s report shows that such figures must be treated with reservation due to the difficulty of differentiating between certain and uncertain cases of cervical pregnancy The mortality nevertheless seems to have declined in recent years, and this clearly demonstrates the importance of blood transfusion in modern obstetrics (Baptisti, 1953)

Conclusion

From a consideration of the literature and our 2 cases we feel that cervical pregnancy can be satisfactorily treated by primary, careful evacuation without curettage combined with tamponade in cases where there is hæmorrhage If the hæmorrhage continues, hysterectomy is indicated

No case treated in this manner has hitherto been published (Sherwin and Berg, 1960)

SUMMARY

Two cases of isthmico cervical pregnancy are reported Both cases were typical with regard to their course and pathological anatomy

Both patients were multiparæ who, apart from several previous intra uterine operations had also had induced abortions Clinically, there was initial painless vaginal hæmorrhage in the second and third months of pregnancy The uterus was enlarged corresponding to the duration of pregnancy and in both cases the external os was dilated and the amniotic sac visible Primary evacuation was performed, using ovum forceps and blunt curette This produced brisk hæmorrhage which did not respond to oxytocics As the hæmorrhage could not be controlled by means of tamponade, hysterectomy was performed in both cases

Examination of the specimens removed at operation revealed that the uterine cavity was empty and only slightly enlarged whereas the cervix was dilated and thin walled with a ragged area corresponding to the placental site

Histological examination showed trophoblastic cells in the region of the cervical glands and decidual reaction in the mucous membrane and the musculature of the cervical region

The ætiology pathogenesis diagnosis, differential diagnosis, pathological anatomy and histology treatment, and prognosis of cervical pregnancy are discussed on the basis of the literature

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been performed in order to ascertain whether this is justified It was, therefore, decided to investigate whether patients with R A fare better after interruption or completion of pregnancy

Case Material

This study was based upon the cases dealt with at the Mothers Aid Centre, Copenhagen, in the period 1955 to 1958 These were 50 patients excluding those with rheumatic fever, osteo-arthritis and non rheumatic diseases

In the spring of 1955 these patients were re examined clinically in their homes or at hospital Four had to be excluded, two because they had emigrated since the original application to the Mothers Aid Centre while one was found to be suffering from gonorrhœal arthritis and one from osteo-arthritis

Table I gives the distribution according to management

Table I *Distribution by Management*

	20 patients had induced abortion
	15 patients had induced abortion + sterilization
	4 patients had spontaneous abortion before decision
	7 patients were refused the permission to have abortion
Total	46 patients

Out of the 46 patients 35 were granted permission to have induced abortion on a medical social indication, 4 miscarried spontaneously *before* the Joint Council had arrived at a decision, but in 3 of these cases the permission was granted

In 7 instances the application was refused and these patients carried their pregnancy to term

In 20 of the cases the chronic joint disease was the main indication for interruption while in the others it was only one factor in the situation Among the 7 cases that were refused R A was the principal diagnosis in 2

Table II shows the distribution of cases in which termination was advised out of the total series seen at the Mothers Aid Centre Copenhagen during the period 1955–1957

Felbo M and Snorrason E, Acta obst. et gynec. Scandinav. 40 116 1961

From the Mothers' Aid Centre (Medical Superintendent H Hoffmeyer) Copenhagen

PREGNANCY AND THE PLACE OF THERAPEUTIC ABORTION IN RHEUMATOID ARTHRITIS

BY

M. FELBO AND E SNORRASON

It is a current opinion that as a general rule pregnancy in patients with rheumatoid arthritis (R A) ought to be interrupted, since it is believed to endanger their health, aggravation of the joint disease having been reported both during and after pregnancy (Clemmesen, 1943, Snorrason, 1950) Temporary improvement may occur during the first months of pregnancy (Davidson, 1950), but the strain of suckling (Clemmesen, 1943, Robinson, 1953) and tending the baby is said to aggravate the prognosis of this more or less rapidly progressing disease

About 40 per cent of all the women applying for induced abortion were granted permission by the Joint Council of the Mothers' Aid Centre in Copenhagen during the period 1955–1957 During the same period the percentage among the women with R A was about 80 per cent both when R A was the main diagnosis and a subordinate diagnosis In setting up the indications, the Joint Council considers all somatic diseases as well as economic, social, and familial factors that may be of significance The same importance seems to have been attached to these factors in the case of patients with R A as in the case of other applicants Comparison of the percentage of granted applications in the two above-mentioned groups shows that the presence of R A has definitely influenced the granting of permission for interruption of pregnancy Up till now no investigation has

Table IV *Time of Onset of R. A*

Age in Years	No of Patients	After Delivery
-25	20	4
26-35	22	9
36-	4	0
Total	46	13

In nearly half the cases the rheumatoid arthritis had set in prior to the 25th year of age, and in 13 cases it started six to twelve months post partum In general about 20 per cent of female patients develop their R A during the first year after delivery (Davidson 1950) but in this series the proportion was 13 out of 46 or almost one third

Before applying to the Mothers Aid Centre for induced abortion 28 out of the 46 patients had borne one or more children

Table V shows that 13 had a history of a total of 37 deliveries *before* they developed R A fifteen had a total of 34 deliveries *while* they had R A and before applying to the Mothers Aid Centre for induced abortion during the period 1955 to 1958

Table V *Deliveries prior to Application to Mothers Aid Centre*

No of Patients	No of Deliveries	No of Patients	No of Deliveries
2	2	3	3
5	19	6	12
4	12	5	15
0	0	1	4
1	5	0	0
1	8	0	0
13	37	15	34
Before R A.		*While* having R A	

The fact that 15 patients had been through a total of 34 deliveries while they had rheumatoid arthritis afforded a possibility of comparing two groups of R A patients one in which the pregnancy was completed and another one in which it was inter-

Table II *Frequency of Indications in the Total Series from the Mothers Aid Centre during the Period 1955–1957*

No. of Applications for Induced Abortion	1955/56		1956/57	
	Absolute Values	Per cent Recommended	Absolute Values	Per cent Recommended
	(Including Hospital Indications)		(Including Hospital Indications)	
Under 25 years	1,444 (36%)	(405) 28%	1,625 (38%)	(376) 23%
25–34 years	1,682 (42%)	(789) 47%	1,702 (40%)	(703) 41%
35 years and over	904 (22%)	(547) 61%	930 (22%)	(4[illegible]) [illegible]
Total	4,030 (100%)[1]	(1,741) 43%	4,257 (100%)[2]	(1,5[illegible]0) [illegible]7%

[1] Including 192 indications decided by hospitals and others

[2] Including 72 indications decided by hospitals and others.

Table III *Age Distribution of the 46 Patients with R. A. from 1955–1957 Who Were Included in the Follow-up*

Age in Years	R A	+ Indication
–25	6	5 (83%)
26–35	22	14 (64%)
36–	18	16 (89%)
Total	46	35 (76%)

Table III gives the age distribution of the 46 patients who were followed up

The patients were classified into three age groups

(1) Patients under 25 years with existing, advanced rheumatoid arthritis persisting from an early age and presenting an extremely serious socio-medical problem due to the probability of progression

(2) Patients between 26–35 years in whom considerable benefit was obtainable from the therapeutic agents now available

(3) Patients aged 35 years and over in whom the disease was a serious socio-medical problem and pregnancy would further complicate this

Table IV shows the grouping of the patients by age at onset of R A

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rupted To the former group may be added 12 patients who had one baby and 4 patients who had two babies during the follow up period despite co-existent R A

Table VI shows the resultant comparable series of R A patients with a history of delivery and R A patients who had induced or spontaneous abortion

Table VI Total Number of Deliveries and Induced Abortions among the Patients with R A

No of Deliveries or Abortions	R. A + Delivery		R A + Abortion	
	No. of Patients	No. of Deliveries	No. of Patients	No. of Deliveries
1	3 + 12	15	35 + 4	39
2	6 + 4	20	3	6
3	5	15	0	0
4	1	4	0	0
Total	31	54	42	45

As mentioned above, 35 out of the 46 patients had been recommended for induced abortion during the period 1955 to 1958, four had a history of spontaneous abortion and 3 of spontaneous or induced abortion up to twice *before* or *during* the period 1955 to 1958 Thus, the total series included 45 cases of abortion in patients with R A and 54 cases in which the pregnancies were carried to term

Result of Follow-up

(a) Prognosis

Certain authors maintain that rheumatoid arthritis improves during pregnancy, especially during its first trimester, only to be considerably aggravated afterwards Progression during the suckling period is said to be characteristic and some authors have recommended mothers with incipient R A to give up suckling (Clemmesen, 1943, Snorrason, 1950) No explanation of the improvement during pregnancy and the subsequent exacerbation has been found Hench (1938) related it to alterations in

serum lipids but subsequent investigations have shown that this theory does not hold (Snorrason 1950) The exacerbation after delivery is more likely to be due to changed hormonal conditions when the body returns to a normal ovarian cycle

Table VII sets out the data supplied by the patients classified by age groups They were questioned regarding the course of their disease both when they completed their pregnancy and when they had it interrupted and the replies were checked in the files of the Mothers Aid Centre Copenhagen It could be ascertained therefore whether the patients had more or less consciously tried to exaggerate at the time of application or at follow up but the answers showed no discrepancies

Table VII R A *Symptoms before during and after Delivery and Induced Abortion Respectively*

		–25 Years		26–35 Years		36– Years		Total	
		Delivery	Abortion	Delivery	Abortion	Delivery	Abortion	Delivery	Abortion
Beginning of pregnancy	improved	0	0	2	0	0	0	2	0
	unchanged	14	2	21	12	7	5	42	19
	worse	2	4	8	9	0	13	10	26
During pregnancy	improved	1	0	13	5	1	2	15	7
	unchanged	7	2	11	10	5	5	23	17
	worse	8	4	7	6	1	11	16	21
After delivery or abortion	improved	0	0	3	0	0	0	3	0
	unchanged	4	1	7	8	4	4	15	13
	worse	12	5	21	13	3	14	36	32
	46 Patients	16	6	31	21	7	18	54	45

A comparison of the three groups shows that after carrying pregnancy to term the disease became worse in the youngest group while a relatively large proportion of the middle and oldest group found their disease unchanged After abortion (spontaneous or induced) the disease was worse in all three groups the exacerbation however being least marked in the middle group

In all three groups the disease was unchanged or improved during the first trimester of pregnancy In the middle age group

this improvement was maintained throughout pregnancy, while in the other two age groups it rapidly decreased

When the groups of pregnancy and abortion are considered as one, it will be seen that in both groups the disease was unchanged' or improved in about one-third of the cases In the group of abortion it is true, there is improvement immediately after the abortion, but both groups show subsequent aggravation in two-thirds Other things being equal this does *not* speak for granting permission to induce abortion in cases of rheumatoid arthritis

The hope of arresting or improving the disease by abortion is a false one, and the therapeutic agents which have become available during recent years ought to be able to arrest exacerbation, if any, after the completion of pregnancy

At follow-up, the patients were divided into four clinico pathological stages of progression (Snorrason, 1951) At the time of follow-up, two to four years after their application to the Mothers Aid Centre, only one-quarter of the 46 patients in capsular Stage I had remained in this stage Out of the Stage II patients, *i e* with partially irreparable capsular changes and incipient cartilaginuous destruction, only one-half remained in this stage *despite* physical therapy combined with chrysotherapy or steroid medication Out of patients in Stage III with partially

Table VIII *Objective Changes in the Patients with R A*

R A + Abortion				R A. + Refusal				Total				Distribution of Arrested Cases
At Application		At Follow up		At Application		At Follow up		At Application		At Follow up		
Stage	No	Stage	No	Stage	No	Stage	No	Stage	No	Stage	No	
		I	2			I	1			I	3	
I	10	II	7	I	2	II	1	I	12	II	8	3 in 12
		III	1							III	1	
II	23	II	10	II	5	II	3	II	28	II	13	13 in 28
		III	13			III	2			III	15	
III	6	III	4	III	0			III	6	III	4	4 in 6
		IV	2							IV	2	
IV	0			IV	0			IV	0			

irreparable cartilaginous and bony changes two thirds remained in this stage during the follow up period

As evident from Table VIII, progression was most pronounced in the early stages among the 39 patients who had induced or spontaneous abortion (The number of patients whose application was refused is too small for numerical evaluation)

Efforts to control the disease must, therefore consist in effective physico medical as well as social measures Since the patients do not seem to fare better after abortion than after delivery (Table VII), the possibilities of steroid and chrysotherapy available to-day must be utilized to the full and combined with effective socio-economic support

In the present series it was regrettably impossible to follow up the cases of completed pregnancy owing to too short a follow up period (six months to two years), but according to the available data (Table VII) there is no reason to give induced abortion priority to completion of pregnancy with adequate help during the post partum period

It has been maintained that patients with R A were more liable to spontaneous abortion than before the onset of their disease

Table IX gives the distribution in the present series There does not appear to be a definite difference before and after the onset of the disease

Table IX R A *and Spontaneous Abortion*

	No. of Pregnancies	Spontaneous Abortion
Before R A	49	12
After R A	42	8

(b) Social Conditions

Various authors have claimed that poor economy and unsatisfactory housing were factors promoting the progression of R A *The disease is* not however as also mentioned elsewhere, peculiar to the lower classes of society (Snorrason 1950), and the

Table X *Influence of Social Factors upon Pregnant Women with R. A*

	Social Conditions	Delivery				Induced Abortion			
		Poor	Medium	Good	Total	Poor	Medium	Good	Total
Disease after delivery or induced abortion	Improved	0	0	3	3 in 3	0	0	0	0 in [illegible]
	Unchanged	7	6	2	15 in 15	7	2	4	13 in 1[illegible]
	Worse	22	7	3	32 in 36	18	8	3	29 in [illegible]
	Total	29	13	8	50 in 54	25	10	7	42 in 4[illegible]

question is now whether pregnancy combined with rather poor social conditions may be a factor of such consequence as to afford an indication for induced abortion

On the basis of the data from the files of the Mothers' Aid Centre at first application and from the follow up visits in the patients' homes, the present study elucidated the problem as shown in Table X

In 50 out of the 54 completed pregnancies and in 42 out of the 45 cases of abortion the social conditions were known It is not surprising that the disease condition was 'worse' when social conditions were poor than when they were medium' or good, but the interesting and essential finding is that *no* difference was found between the groups of completed pregnancy and of induced abortion as regards the development of R A

Fifteen out of the 42 patients whose socio medical data were known, had sterilization at the time of induced abortion There is a striking frequency of sterilization among patients in socially good circumstances (Table XI)

Table XI *Frequency of Sterilization among R A Patients of Different Social Strata*

	Social Conditions	Poor	Medium	Good
Disease after induced abortion	Improved	0	0	0
	Unchanged	3 in 7	2 in 2	4 in 4
	Worse	9 in 18	1 in 8	2 in 3
	Total	12 in 25	3 in 10	6 in 7

Discussion

Several authors have claimed that rheumatoid arthritis improves during and for varying periods of time after a pregnancy, only to become exacerbated afterwards Moreover, it has been reported that rheumatoid arthritis frequently arises during the first six to twelve months after completion of a pregnancy (especially in cases with familial predisposition) As a result nearly 80–90 per cent of patients with the combination pregnancy and rheumatoid arthritis have so far been granted permission to have induced abortion on a medical or socio-medical indication

The results of the present study show that the prognosis is not better after induced abortion than after completed pregnancy – if anything the reverse holds good It shows also that if reasonably good social conditions can be afforded to the severe cases during and after the pregnancy, this offers a better prognosis than does induced abortion with unchanged social conditions

It will be seen from Table VII that the joint disease improved or stayed unchanged in a large proportion of the patients during the first trimester or throughout pregnancy This was most pronounced in the age group 26–35 years in which two-thirds obtained temporary improvement The same applied also to the patients who were granted induced abortion Progression takes place after delivery but also after induced abortion Intensive medical and physical therapy is indicated therefore during the first year after delivery or after interruption of pregnancy

Moreover it is evident from Table X that the tendency to exacerbation and progression is less marked among women in the more well to-do classes of society

Among the complex of circumstances (medical social and familial) that make up the indication for induced abortion the tendency to progression and development of rheumatoid arthritis carries great weight According to the present results however the women should be advised to complete their pregnancy when social conditions are or can be rendered satisfactory

Considering the therapeutic possibilities available now the

aim must be to improve the social and familial factors during the first year or two after delivery That it is essential to keep an eye on the disease after childbirth is clearly shown by the present series (Table IV) in which 13 out of 46 patients developed their rheumatoid arthritis during the first year post partum On the other hand, it shows also (Table V) that some women have a history of up to 8 childbirths before the onset of their rehumatoid arthritis

SUMMARY

Out of 46 patients with rheumatoid arthritis who applied to the Mothers' Aid Centre, Copenhagen, for permission to have abortion induced during the period 1955–1958, 35 were granted this permission, while 7 were refused, and 4 had spontaneous abortion

Follow up of 45 cases of rheumatoid arthritis from two to four years after legal abortion, compared with 54 women with rheumatoid arthritis who had completed their pregnancies, showed that – other things being equal – the chances for the women's health are nearly the same, whether induced abortion is performed or they carry on with their pregnancies The one proviso is that their circumstances, *i e* the socio medical con ditions, must be rendered as favourable as possible for a year or two following delivery

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THE PRACTICAL VALUE OF ELECTRO-ENCEPHALOGRAPHY IN PRE ECLAMPSIA AND ECLAMPSIA

BY

PER KOLSTAD

The observation of Berger (1929) that it is possible to record changes of electrical potential occurring in the human brain, has thrown much new light upon disorders of cortical function Abnormal electro encephalograms (EEG) may be found both in organic and functional brain diseases It is now well known that an epileptic seizure is accompanied by a disturbance in the normal electrical activity of the brain Clinically the convulsions of epilepsy and eclampsia are the same The present article concerns the practical value of EEG studies in pre-eclampsia and eclampsia

Maltby and Rosenbaum (1942 1943) found cerebral dysrhythmia in 13 of 20 patients with eclampsia against 2 of 20 controls They suggest that there exists a primary cerebral dysrhythmia in women with eclampsia and that the associated toxæmia may be the trigger mechanism that exaggerates the inherent dysrhythmia to the degree that convulsions occur In their terminology eclamptic patients without dysrhythmia suffer from eclampsia toxica and when pre-eclamptic toxæmia supervenes in a patient with dysrhythmia it gives rise to eclampsia reflectoria

Gibbs and Reid (1942) carried out EEG studies on 28 pregnant women They described a slowing of cortical activity and

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Follow-up of 45 cases of rheumatoid arthritis from two to four years after legal abortion, compared with 54 women with rheumatoid arthritis who had completed their pregnancies, showed that – other things being equal – the chances for the women's health are nearly the same, whether induced abortion is performed or they carry on with their pregnancies The one proviso is that their circumstances, i e the socio medical conditions, must be rendered as favourable as possible for a year or two following delivery

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McIntosh (1952) likewise is of the opinion that persons with cerebral dysrhythmia are more prone to develop eclamptic convulsions He found cerebral dysrhythmia in 5 of 6 patients with eclampsia The records were made several days after the last eclamptic fits Moracci (1954) observed that morphine affected the EEG in pregnant women, contributing to the appearance of changes characteristic of irritative cortical lesions Therefore he uses no morphine in the treatment of eclampsia His series consists of 64 pregnant women, 19 showed a slight dysrhythmia and 6 showed marked EEG changes This author also claims that toxæmia of pregnancy may act as a precipitating factor in latent cases giving rise to convulsions Poidevin (1955) published EEG studies of 98 pregnant women EEG s were taken ten to fourteen days after delivery in 12 eclamptic patients and most of the others also were investigated post partum He observed dysrhythmia in 24 per cent of the patients with toxæmia and in 83 per cent of eclamptic patients, against 15 per cent of the normal controls Fifteen cases with essential hypertension showed a dysrhythmia frequency of 26 per cent Thirthy three cases with toxæmia were divided into groups with mild moderate and serious toxæmia There seemed to be no connection between the degree of toxæmia that is, the blood pressure elevation and abnormalities of cerebral rhythm Kotasek and Lesny (1957) however, found cerebral dysrhythmia in 19 6 per cent of healthy pregnant women against 50 per cent of patients with moderate, and 87 per cent of those with severe toxæmia Hootsmans and van Prooije (1957) stress the well known fact that there is no clear relation between the degree of toxæmia and occurrence of convulsions but on the other hand they observed abnormal EEG patterns in 11 of 22 eclamptic patients while only 5 of 18 patients with toxæmia showed cerebral dysrhythmia The tracings of the eclamptic patients were made seven to twenty five days after the last seizure In only one case an EEG had been recorded two days before convulsions started and no special abnormalities are described in this case The authors however conclude that EEG is of practical value in preventing eclampsia

Douglass *et al* (1953) claim that there is no connection

an absence of high voltage fast activity in normal pregnancy In 4 of 8 patients with pre-eclampsia an abnormal fast activity was found, and the authors concluded that the EEG may disclose a sub-convulsive state, and therefore is of practical value Whitacre *et al* (1947) believe that the abnormal EEG pattern in eclampsia is due to anoxæmia of the brain In one case an EEG was taken during and after eclamptic convulsions, and this case is described in detail Twelve days post partum the EEG was normal

Jost (1948) studied EEG patterns in relation to blood pressure changes in eclampsia He claimed that the EEG may become normal when the blood pressure is lowered using caudal analgesia or veratrum viride Thirty-three EEG records were made on 9 patients during and after eclamptic seizures In one of these cases the EEG taken three days before eclampsia and birth was entirely normal Neuweiler (1949) is of the opinion that some patients are disposed to get convulsions when toxæmia supervenes, and this disposition may be discovered by EEG He has, however, no personal series Parviainen *et al* (1950) report on the effect of ammonium chloride upon EEG changes in toxæmia of late pregnancy Six patients with severe pre eclampsia were treated with ammonium chloride 4 g daily Two patients with marked cerebral dysrhythmia showed a return to normal of the EEG after a few day s treatment

Roubillard and Villavicencio (1950) observed an abnormal EEG in 20 of 23 patients with eclampsia and in 6 of 26 with pre-eclampsia In eclamptic patients the records were taken about twenty-four days after the last convulsion, and in pre eclamptic patients one to ten days before delivery Several weeks later both groups were checked again The abnormality persisted unchanged for weeks and months The authors believe that toxæmia of pregnancy precipitates convulsions in pre-disposed women, and that such a predisposition can be demonstrated by EEG Therefore an EEG should be taken in pregnant women with a family history of convulsions and in patients with pre eclampsia They conclude that cerebral dysrhythmia not responding to treatment is an indication for administration of anticonvulsant drugs or induction of labour

condly, we wanted to get a wider personal experience concerning the types of cerebral dysrhythmia occurring in pre eclampsia EEG patterns described as dysrhythmia may be very different, and it is now generally accepted that as many as 10–20 per cent of normal persons show a slight dysrhythmia

Series

In the Gynæcological Department of Vestfold Sentralsykehus there are about 950 deliveries each year, and only 2–3 patients with eclampsia During the last year EEG records were made on 2 eclamptic women These 2 cases are very illustrative, and this series is published in spite of it being small consisting of 27 EEG tracings from 17 patients

Table I *EEG Findings in 17 Patients with Pre-eclampsia and Eclampsia*

Diagnosis	No of Patients	Abnormal EEG
Mild pre-eclampsia	3	1
Severe pre-eclampsia	11	3
Eclampsia	2	2
Essential hypertension	1	1
Total	17	7

As shown in Table I 1 of 3 patients with mild eclampsia and 3 of 11 with severe pre-eclampsia had EEG abnormalities One woman with essential hypertension and super imposed toxæmia also showed cerebral dysrhythmia The 2 patients with eclampsia will be described in detail later Ten patients were primigravidæ, and the majority suffered from severe toxæmia Three cases were delivered by Cæsarean section and in 9 patients some other operative procedure or induction of labour had to be performed Four children died *in utero* about one month before term If possible EEG records were always made *before* treatment was initiated

between cerebral dysrhythmia in early pregnancy and the development of toxæmia Patients with definitely abnormal tracings do not develop more severe toxæmia than those with normal brain patterns, but if EEGs were taken from all pregnant women, they might aid in predicting in which women eclampsia may develop

In contrast to the above mentioned authors, Bärtschi (1957) and Geiser-Rauch (1958) doubt that a close relationship exists between cerebral dysrhythmia and eclampsia Fourteen women who had suffered from eclampsia in the previous few years, were submitted to EEG examination made at rest, during hyperventilation and after triple activation (Cardiazol, Narconumal, and flicker) The results were compared with a group of 50 normal controls No significant difference was found

Burnett (1946) in an excellent survey on the problem of epilepsy and pregnancy, did not find that eclampsia is more common among epileptics, 6 of 19 epileptics investigated by him developed toxæmia during pregnancy Three of these had more frequent epileptic fits, while the 3 other toxæmia patients seemed to be unaffected, and none of them developed eclampsia

On analysing these reports most authors agree that an EEG is of practical value, disclosing pregnant women with a pre-disposition to convulsions Cerebral dysrhythmia in pre-eclamptic women may be an indication for more active therapeutic measures, *e g* induction of labour In our opinion, however, there is not sufficient evidence to make this conclusion from any of the studies hitherto published The EEG recordings on eclamptic patients almost always have been made *after* convulsions and delivery *Cerebral dysrhythmia following eclamptic seizures* may easily be explained by *e g* cerebral hæmorrhages, anoxæmia of the brain, or cerebral œdema Nor has anybody proved that eclampsia is seen more often in pre-eclamptic women with cerebral dysrhythmia than in those without

To throw some light upon the question as to whether it is possible by means of an EEG to predict an eclamptic attack, we have made EEG studies on a small number of pre eclamptic patients Our first aim has been to obtain an EEG record *before* delivery, and, if possible, close to the time of eclamptic fits Se-

condly, we wanted to get a wider personal experience concerning the types of cerebral dysrhythmia occurring in pre-eclampsia EEG patterns described as dysrhythmia may be very different, and it is now generally accepted that as many as 10–20 per cent of normal persons show a slight dysrhythmia

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Table II *Blood Pressure and EEG Abnormalities*

Blood Pressure On Recording EEG	Highest Level Measured	EEG-findings
110/75	(180/105)	Marked dysrhythmia, generalized
110/85	(180/105)	Marked focal dysrhythmia
120/80	(160/100)	-
120/80	(160/110)	-
130/90	(190/110)	Slight generalized dysrhythmia
130/100	(130/100)	Diffuse theta activity
145/100	(145/100)	-
150/90	(190/110)	Dysrhythmia r temporal region
150/100	(170/115)	-
145/105	(175/115)	-
150/105	(175/110)	Temporal theta activity
160/100	(180/125)	-
160/110	(190/120)	Slight generalized dysrhythmia
160/120	(160/120)	-
170/115	(170/115)	-
175/105	(175/105)	Temporal theta activity
175/110	(175/110)	Temporal theta activity
185/110	(220/130)	-
185/130	(200/130)	-
190/110	(190/110)	-
190/130	(240/145)	Generalized dysrhythmia
190/135	(190/135)	-
220/130	(220/130)	-

There is no correlation between blood pressure elevation and EEG abnormalities in our series As shown in Table II dysrhythmia was observed both in patients with normal and high blood pressure, and the higher levels were not accompanied by more marked cerebral dysrhythmia This agrees with the observation of Poidevin (1955), but not with the findings of Jost (1948)

Nor does there seem to be any relation between the degree of œdema, proteinuria or cerebral symptoms and the EEG This is illustrated in Table III Patients with severe pre-eclamptic symptoms may have normal EEG tracings, while patients with a less alarming clinical picture may have marked EEG disturbances

Table III *Pre-eclamptic Symptoms and EEG Findings*

Headache Visual Disturbances	Oedema	Proteinuria ‰	EEG Abnormalities
—	++	1	+
—	++	1½	+
—	++	2	—
+	+	¼	—
+	+	2	++
+	+	5	—
+++	—	¼	+++
+	++	1½	—
+	++	3	—
+	+	3¹/	+
++	++	3	—
+	+++	3½	—
++	++	4½	—
++	+++	4	—
+++	++	4	—
+++	++	6	+
+++	+++	9	—

Case Reports

Case 1 A I 34 years para III was admitted with severe pre-eclamptic symptoms about one month before term She complained of intense and persistent headache visual disturbances œdema of the feet ankles hands and face Routine pregnancy examination three weeks earlier was normal B P 190/110 and massive proteinuria 9 ‰ on admittance Ophthalmoscopy disclosed optic nerve œdema The symptoms indicated that convulsions were imminent However an EEG was taken before treatment was started and no abnormalities were found (Fig 1)

The patient was treated with sedatives intravenous hypertonic glucose diuretics and bed rest There was a slight but definite clinical improvement Nevertheless 38 hours after admittance convulsions occurred followed by coma lasting a few hours Fœtal heart sounds could not be heard after the eclamptic attack An EEG taken four days later was abnormal with signs of organic cerebral disorder mostly confined to the right temporal region (Fig 2) The abnormalities persisted unchanged for about one week Three weeks after convulsions the EEG was normal again.

Case 2 A L O 22 years para II Uncomplicated delivery at 18 years of age Seen when six and a half months pregnant. Less than two hours before hospitalization she had generalized convulsions followed by coma There were no preceding symptoms except slight abdominal pain the day before On

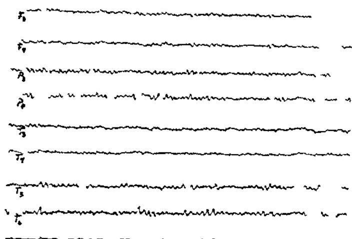


Fig 1 Case 1 Normal EEG 38 hours before convulsions.

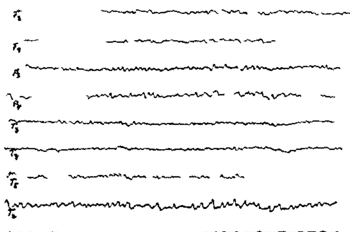


Fig 2 Case 1 EEG 4 days after eclampsia Dysrhythmia mostly confined to the right temporal region

examination the blood pressure was found to be 110/85 (post-eclamptic shock?) there was no oedema but a trace of protein in the urine The tongue was bitten with blood around the mouth Neurologic examination including ophthalmoscopy was negative except that the patient showed slow cerebration and some disorientation There was retrograde amnesia No family history of epilepsy or convulsions was elicited An EEG taken six hours after the eclampsia disclosed marked signs of organic disturbances localized especially to the right parieto-occipital region (Fig 3) Ten days later labour pains started At the same time the blood pressure rose to 160/105

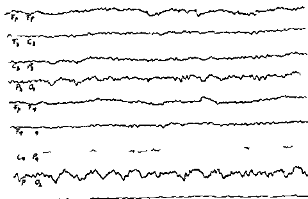


Fig 3 Case 2 EEG 6 hours after first eclamptic attack Marked dysrhythmia localized especially to the right parieto-occipital region

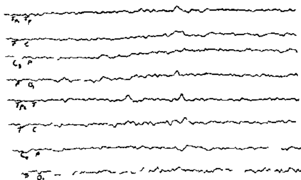


Fig 4 Case 2 EEG 12 days after first and 2 days after second eclamptic attack More marked generalized dysrhythmia but also focal signs right parieto-occipital region

and the patient complained of headache and visual disturbances Ophthalmoscopy was negative Hypertonic glucose and sedatives were given. The next day she gave birth to a premature child weighing 1 240 g The placenta had to be removed manually Two hours later she once more complained of headache and suddenly convulsions occurred lasting four minutes Another EEG was taken two days after this attack and showed the same abnormalities in the right parieto-occipital region but now also more marked generalized dysrhythmia could be seen (Fig 4)

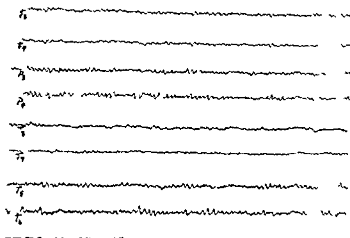


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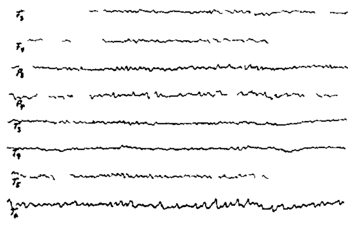


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and slight EEG abnormalities seem to be more common in patients with pre-eclampsia than in normal controls *An abnormal EEG must, however, always be interpreted in relation to the clinical picture*

It is of great practical interest to follow patients after eclampsia with EEG tracings to see if signs of organic cerebral disorders persist In our two patients, the abnormalities disappeared three weeks and two months after the eclamptic attack On the other hand, it would be of great theoretical interest if EEG studies could help discover the trigger mechanism which initiates the convulsions in eclampsia It would be desirable to record the EEG continuously before during and after convulsions in a large series of patients This, however, would be a difficult, if not impossible task Concerning the EEG abnormalities in our 2 patients with eclampsia neither of them showed specific epileptiform potentials It is a little surprising that in both cases marked *focal* dysrhythmia was observed (Figs 2 and 3)

SUMMARY

The literature concerning EEG and toxæmia of pregnancy is reviewed A series consisting of 27 EEG records on 15 patients with pre eclampsia and 2 with eclampsia is presented EEG abnormalities were found in 5 of the pre eclamptic patients One woman with eclampsia showed normal EEG tracings thirty-eight hours before convulsions and focal dysrhythmia after eclampsia In the other eclamptic patient marked focal dysrhythmia was observed six hours after convulsions EEG disturbances persisted three and eight weeks after convulsions, but in both cases the EEG returned to normal No correlation was found between EEG abnormalities and blood pressure proteinuria, œdema, cerebral symptoms or ophthalmoscopic findings It is concluded that EEG is of little use in predicting an eclamptic attack EEG must always be interpreted in relation to the clinical manifestations of pre eclamptic toxæmia

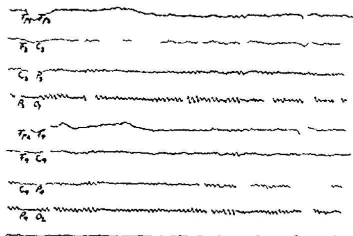


Fig 5 Case 2 Normal EEG 2 months after first eclamptic attack

The patient was followed with EEG control and abnormalities were found as late as one month after her second eclamptic attack After two months however the EEG record was entirely normal (Fig 5) The blood pressure became normal the day after her second seizure but slight proteinuria persisted for two weeks Ophthalmoscopy never disclosed anything pathological

Discussion

Case 1 seems to show that EEG examination is of little or no value in predicting an eclamptic attack No EEG abnormalities were found thirty eight hours before eclampsia in spite of severe pre eclamptic symptoms No treatment had been given when the tracings were made When we correlate this case and the rest of our series with the literature, our statement seems to be confirmed Several authors suggest that eclampsia *may* be prevented by EEG examination but none claim that they really *have* prevented eclamptic fits by EEG studies Jost (1948) and Hootsmans and van Prooije (1957) *e g* both mention cases with normal tracings a few days before convulsions In our opinion it is not justifiable to rely on EEG records when treatment is being decided in cases of pre eclampsia Abnormal EEGs may be seen in mild cases, and normal records in severe cases There is no correlation between the clinical manifestations and the EEG except that marked dysrhythmia may appear *after* eclamptic fits

Weber Jan Acta obst et gynec Scandinav 40 139 1961

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THE SITE OF PRODUCTION OF GONADOTROPHIN IN THE PLACENTA AT TERM

A Histo chemical Study

BY

JAN WEBER

While it had previously been assumed that the gonadotrophic hormone which is excreted in the urine of pregnant women, was formed in the pituitary Philipp (1929 1930) demonstrated in transplantation experiments on infantile female mice that its site of production is in the placenta

This observation was later confirmed by further transplantation experiments (Kido 1937 Guldberg 1936) and by the demonstration of gonadotrophic action of placental extract (Smith and Smith 1935) Finally, Gey *et al* (1938) successfully cultivated placental cells *in vitro* for several months and showed that these cells formed gonadotrophin

It is generally assumed that the production of gonadotrophin occurs in the Langhans cells This assumption is based mainly upon the observation that the formation of gonadotrophin is most pronounced within the first few months of pregnancy, during which time the Langhans layer also shows the greatest development (Philipp 1930) Moreover, the cells of gonadotrophin producing tissue cultures appear to be morphologically related to the Langhans cells (Jones *et al* 1943)

However the Langhans layer is normally absent towards the

Acknowledgements

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The PAS reaction shows that mucopolysaccharides are present This reaction is therefore not specific for gonadotrophin, since it gives a positive response, for example in the presence of glycogen However the strongly positive reaction in the trophoblastic cells of the septa and in the region of the basal plate suggests that these cells are the site of production of the placental gonadotrophic hormone (Wislocki, 1951, Bargmann, 1957, Thomsen and Willemsen, 1959)

While the PAS reaction demonstrates the carbohydrate group which is attached to gonadotrophin methods of demonstrating nucleic acid compounds are based on knowledge of the cellular processes which are intimately related to protein synthesis

In all protein producing cells accumulation of RNA occurs in the cytoplasm (Caspersson, 1947) This is seen in cell division (Caspersson 1939), during the regeneration of nerve cells after functional activity (Einarson, 1956), in liver cells (I a gerstedt 1949) and in glandular cells producing a protein containing secretion (Oram, 1955 Weber, 1958)

Thus, even though demonstration of intense nucleic acid metabolism in a given cell only shows that protein synthesis occurs in that cell the demonstration of RNA in certain placental cells is of significance in the solution of the problems related to the production of gonadotrophin In view of the close relationship of gonadotrophin and proteins, this production will occur only in cells with a relatively high content of cytoplasmic RNA This fact excludes most placental cell types with minimal basophilia as possible sources of gonadotrophin production but suggests that the trophoblastic cells of the basal plate and the septa may be responsible

It is therefore of interest to study these cells by means of a staining method which is specific for nucleic acid Einarsons gallocyanin chromalum staining is very suitable for this purpose (For a detailed description of the theoretical basis for this staining method and its application the reader is referred to Einarsons (1932) original paper and to a series of subsequent studies published by Einarson and his co-workers)

end of pregnancy, although a few cells of the Langhans' type seem to persist at term (Wislocki and Bennet, 1943) Under special circumstances, for example in anoxic conditions, these cells are reported to be the starting point of a regeneration of the Langhans' layer (McKay *et al*, 1958, Scott, 1958, Hughes, 1959, Jeffcoate and Scott, 1959)

During recent years histo-chemical methods have been used in the study of the placenta, and these have opened the possibility of a better understanding of the various functions of this organ and have aroused renewed interest in the problems related to the formation of gonadotrophin

Dempsey and Wislocki (1945) seem to be the first investigators who subjected the basophilic substance of placental cells to a close evaluation By their studies attention was attracted to the basophilic substance in the trophoblastic cells which are seen as islands in the placental septa As distinct from the syncytial cells, these preserve their basophilic properties till term Treatment with ribonuclease showed that the basophilic substance consisted of ribonucleic acid (RNA)

By similar methods, Ortmann (1949, 1954) showed that the trophoblastic cells in the placental septa and in the region of the basal plate contained RNA At the same time, nuclear changes suggested that an intense secretory process occurred in these cells

The literature on the trophoblastic cells of the basal plate is meagre, which is presumably due to the fact that these cells have often been confused with adjacent decidual cells However, the two cell types differ in that the trophoblastic cells are highly basophilic, while the decidual cells are but poorly stained with basic dyes Moreover, the two cell types differ in their response to periodic-acid-Schiff (PAS) treatment, the decidual cells are only weakly positive, while the trophoblastic cells give a strongly positive PAS reaction (Wislocki, 1951)

The chemical composition of chorionic gonadotrophin is not fully known It is usually thought to be a glycoproteid Newer investigations seem to show that it consists of a carbohydrate fraction, which may be removed without simultaneous disappearance of the biological action of the hormone, and a relatively low-molecular polypeptide (Nielsen, 1957)



Fig 1 Light stromal cells Syncytial cells with slightly stained cytoplasm and widely spaced nuclei Gallocyanin chromalum. × 500

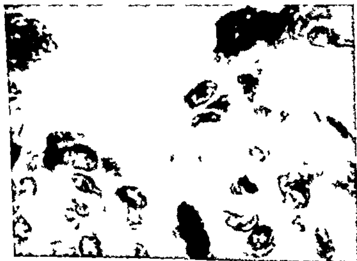


Fig 2 Syncytial cells with widely spaced nuclei and light cytoplasm Gallocyanin chromalum × 1250

Material and Methods

Placentæ from women who went to term after uncomplicated pregnancies, were used in the study

The tissue which was studied histologically consisted of thin slices cut at a right angle to the maternal surface Fragments were removed from three different areas on the maternal surface, both centrally and peripherally

The tissue was fixed in Carnoy's solution and embedded in paraffin Sections of a thickness of 5 μ were stained by Einarson's gallocyanin-chromalum method

Results

In sections treated with gallocyanin chromalum only the cellular elements which contain nucleic acid are stained The nuclear chromatin of all cell types is stained, since it consists of desoxyribosenucleic acid (DNA), whereas the cytoplasm does not take any stain unless it contains RNA

The cytoplasm of the cells of the villous stroma does not stain at all, which shows that it does not contain nucleic acid The surface of the villi is lined by a single layer of syncytial cells, whose nuclei are often widely interspaced (Fig 1) The cytoplasm between the nuclei is almost unstained (Fig 2) In some areas, the villous epithelium reveals accumulations of nuclei, so that it assumes a stratified appearance (Fig 3) These accumulations of nuclei in the syncytial layer result in the formation of the so-called syncytial knots, which are a characteristic feature of the mature placenta (Fig 4) The significance of these syncytial knots is unknown, nor is it known if they are formed by migration of the nuclei or by proliferation of the syncytial layer in these places The fact that mitoses are absent suggests that they are formed by migration of the nuclei, but it cannot be ruled out that they may be due to amitotic cell division

Functionally, the diminished density of nuclei in the syncytial layer may indirectly be of importance in the exchange of substances between the vessels of the villi and the intervillous spaces since these two vascular systems are often separated only by

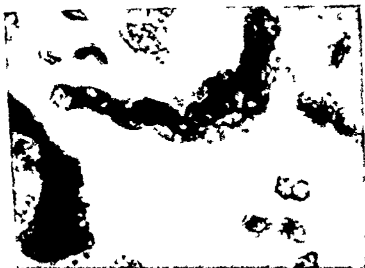


Fig 5 Syncytial knots with sparse amounts of cytoplasm Gallocyanin chromalum × 1250



Fig 6 Langhans cell with light cytoplasm Gallocyanin chromalum × 500

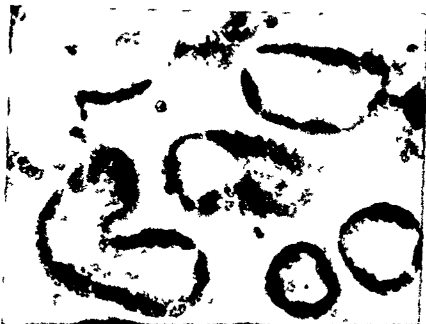


Fig 3 Syncytial cells with accumulated nuclei Gallocyanin chromalum × 500



Fig 4 Formation of syncytial knots Gallocyanin chromalum × 500

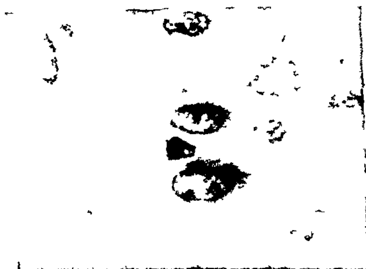


Fig 9 Trophoblastic cells of the basal plate with large nuclei showing intense staining of the nuclear membrane and RNA-containing cytoplasm Gallocyanin chromalum × 1250

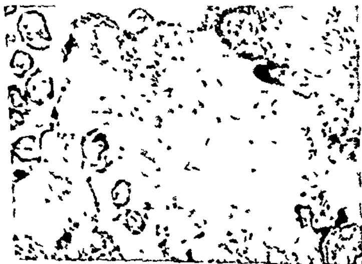


Fig 10 Trophoblastic cells of the septum in the villous layer Gallocyanin chromalum × 1250



Fig 7 The villous layer and the trophoblast in the region of the basal plate Gallocyanin chromalum × 125

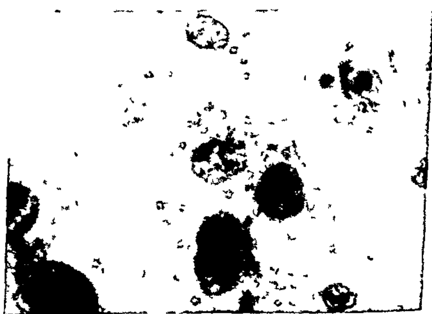


Fig 8 Trophoblastic cells of the placental site with RNA-containing cytoplasm Gallocyanin chromalum × 1250

hans cells have a cytoplasm which stains only very poorly with gallocyanin chromalum showing that their RNA content is only slight Accordingly, these cells can hardly be the site of production of a protein containing secretion

Between the boundary of the intervillous space and the decidua basalis there is a layer of trophoblastic cells which morphologically and histo-chemically differ distinctly from the afore mentioned cells (Fig 7) These trophoblastic cells are large and have large nuclei (Figs 8 and 9), their cytoplasm stains heavily with gallocyanin chromalum A large nucleolus is often present, and intense staining of the nuclear membrane is seen in some places Morphologically and histo-chemically, these cells reveal properties similar to those which may be observed in cells which produce a protein containing secretion or otherwise take an active part in protein synthesis

Exactly the same conditions may be observed in the trophoblastic cells which lie in the placental septa (Figs 10 and 11) This type of trophoblastic cell does not seem to differ from those in the basal plate as regards histo-chemical, morphological and functional properties

Discussion

Histo-chemical methods are suitable to detect the placental cells which are the site of production of gonadotrophin The PAS reaction which has been used in previous studies is not specific for gonadotrophin and therefore, cannot solve the problem

Recent studies have shown that the cytoplasm of the trophoblastic cells in the placental site and the septa contain RNA This property is found only in cells which synthetise proteins and is always present in such cells

In view of the chemical relationship between gonadotrophin and proteins (polypeptides) it must be assumed that gonado trophin is formed in cells whose cytoplasm contains RNA and that cells in which cytoplasmic RNA is absent can hardly be the site of production of this hormone

Einarson s gallocyanin chromalum staining method is specific for nucleic acids and the staining intensity depends exclusively



Fig 11 Trophoblastic cells of the septum with large nucleoli and RNA containing cytoplasm Gallocyanin chromalum × 500

the endothelium of the villous vessels and the thin layer of cytoplasm in the syncytial layer The accumulation of nuclei with formation of syncytial knots is usually considered to constitute one of the age phenomena of the placenta

The nuclei in the knots often take an intense stain in gallocyanin stained sections Coarse chromatin granules are evenly distributed in the karyoplasm (Fig 5) It is difficult to distinguish the cytoplasm between the closely packed nuclei

In a few places cells are situated closely beneath the syncytial layer Morphologically these cells are similar to the Langhans cells As their cytoplasm is unstained they do not contain RNA (Fig 6) It must be assumed that they represent remants of the Langhans layer

Thus none of these cell types shows signs of intense protein synthesis The cells in the syncytial knots contain only sparse amounts of cytoplasm which renders it unlikely that formation of protein like substances could occur in these cells The other syncytial cells the stromal cells and the persistent Lang

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on the concentration of cytoplasmic nucleic acid Both these properties are absent in the basic dyes in common use, which are therefore unsuitable for the demonstration of nucleic acid

A study of placental tissue by means of this staining method revealed that the trophoblastic cells in the placental site and in the septa are the only cells which have appreciable amounts of nucleic acid in the cytoplasm As these cells also show other signs of intense protein synthesis, it must be assumed that they are the site of production of chorionic gonadotrophic hormone

SUMMARY

The literature on the histo chemistry of the trophoblastic cells in the basal plate and the placental septa is reviewed with special reference to the content of ribonucleic acid

As gonadotrophin is protein in nature, it must be assumed that it is produced in cells which present the morphological and histochemical properties which are characteristic of protein synthesis, of which one of the most conspicuous is the presence of ribonucleic acid in the cytoplasm

By Einarson's gallocyanin chromalum staining method it was shown that the trophoblastic cells in the basal plate and the septa are the only cells in the mature placenta which contain a high concentration of ribonucleic acid

Accordingly, it must be assumed that gonadotrophin is formed by these cells during the last months of pregnancy

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that the excess histamine in the mother s urine had its origin in the fœtus, which was found to produce histamine at a very high rate (Kahlson, Rosengren, Westling, and White, 1958)

The present paper describes observations on the urinary excretion of histamine during pregnancy and in the puerperium in humans In addition some observations on the histamine content of blood from the mother and from the umbilical vessels of the child will be mentioned

Methods

Urine Urine was collected in 24 hour specimens Immediately after each voiding the urine was transferred to clean glass bottles containing 10–15 *ml* 10 N *HCl which brought the pH* of the collected specimen below 2 Histamine was extracted from the urine as described by Duner and Pernow (1956) A 100 ml aliquot of the 24 hour specimen was adjusted to pH 6 5 with NaOH and then allowed to pass through a cat ion exchange resin (Amberlite IRC-50 the column measuring 9 by 100 mm) Histamine was eluated from the column with HCl The acid eluate was brought to pH 7 4 with NaOH and, as a rule used directly for assay on the guinea pig ileum The biological assay was performed on isolated guinea pig ileum suspended in a 4 ml bath containing Tyrode s solution One litre of the Tyrode s solution contained 8 0 g NaCl, 0 2 g KCl, 0 2 g $CaCl_2$ 1 0 g $NaHCO_3$ 0 05 g NaH_2PO_4 0 1 mg atropine sulphate and 0 15 g glucose The sensitivity of the ileum was such that good responses were obtained with histamine in doses of about 0 01 μg of the base

The recovery of histamine added to the urine before neutralization and absorption on the ion exchange column was 70 ± 5 3 per cent (mean of 17 observations ± S E M) This figure is similar to those obtained by Duner and Pernow (1956) and Roberts and Adam (1950) The recovery was tested in urine samples having a histamine content of their own which varied between 17 and less than 0 40 μg histamine base per 100 ml of urine The percentage recovery of small amounts of histamine from urines containing very little histamine tended

Bjurö T Lindberg S and Westling H., Acta obst et gynec Scandinav 4 152, 1961

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OBSERVATIONS ON HISTAMINE IN PREGNANCY AND THE PUERPERIUM

BY

T BJURÖ S LINDBERG AND H WESTLING

There are several observations which point to a connexion between histamine and pregnancy Histamine causes a contraction of uterine smooth muscle in several species (Dale and Laidlaw, 1910, and others) Measurement of the plasma concentration and urinary excretion of histamine, however, have failed to give evidence of a role for histamine in parturition in the human female (Wicksell, 1949 b) Another experimental finding which indicates, although indirectly, that histamine may be concerned in pregnancy is the high histaminolytic activity of the placenta in several species (Swanberg, 1950, and others) In man there is also a concomitant increase in the histaminolytic activity of the plasma (Ahlmark, 1944, Wicksell, 1949 a) So far it has not been possible to prove that the increased histamine inactivation in placenta and plasma *in vitro* is of any importance in regard to the effects of histamine or the metabolism of injected histamine by the pregnant woman (Nilsson, Lindell, Schayer, and Westling 1959) But it is possible that placental tissue and plasma may be active in the metabolism of endogenous histamine, produced e g by the fœtus

Recently it was found that rats excrete large amounts of histamine in the urine during the later part of pregnancy (Kahlson, Rosengren, and Westling 1958) Evidence was obtained

hat the excess histamine in the mother's urine had its origin in he fœtus, which was found to produce histamine at a very high ate (Kahlson, Rosengren, Westling, and White, 1958)

The present paper describes observations on the urinary excretion of histamine during pregnancy and in the puerperium in humans In addition some observations on the histamine content of blood from the mother and from the umbilical vessels of the child will be mentioned

Methods

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The recovery of histamine added to the urine before neutralization and absorption on the ion exchange column was 70 ± 5 3 per cent (mean of 17 observations ± S E M) This figure is similar to those obtained by Duner and Pernow (1956) and Roberts and Adam (1950) The recovery was tested in urine samples having a histamine content of their own which varied between 17 and less than 0 40 μg histamine base per 100 ml of urine The percentage recovery of small amounts of histamine from urines containing very little histamine tended

to be lower than in the other experiments, but it was never below 48 per cent

It was felt that the biological assay of histamine in urine extracts containing small quantities histamine (below 1 μg per 100 ml) was sometimes not reliable, because of an unspecific depression of the contractions of the gut, which could lead to an underestimation of the actual histamine content This could explain the somewhat lower recovery rates of small amounts of histamine from such urines Such an interference with the bioassay could be caused by, among other things, salts in the extracts Precipitation of salts by ethanol acetone as described by Duner and Pernow (1958) was not successful in our hands but extraction of the urinary histamine with butanol, as described by Kahlson *et al* (1958 a) seemed to eliminate the interfering agents, and led to an increase in histamine activity of 20–30 per cent This procedure was, however, not applied routinely and for this reason we regard values for histamine excretion below 10 μg per 24 hours as somewhat uncertain

All values for histamine in this paper refer to free histamine in terms of the base Values for urinary excretion are given as μg per 24 hours Antihistaminic agents, such as chlorpromazine and promethazine, were not given to any patient whose blood or urinary histamine was measured

Blood Blood samples were taken with dry syringes and immediately transferred into vessels containing 10 per cent trichloroacetic acid The histamine content of whole blood was determined according to Code (1937) The recovery rate of the method was 79 per cent (mean of 5 determinations) Blood from the umbilical vessels was also taken in syringes, avoiding contact with tissue surfaces Heparin or citrate was not used Values for blood histamine are given as μg base per litre of whole blood

Identity with histamine The gut contracting substance in blood and urine, here referred to as histamine, had the following properties in common with histamine

(1) Its activity on the gut was depressed by mepyramine to the same degree as the action of histamine (Reuse, 1948)

(2) On paper chromatography of butanol extracted urine

samples a diazo reacting spot was obtained which had the same Rf value as histamine It was found that all of the gut contracting activity of the urine could be recovered from corresponding areas of paper strips that had not been treated with the diazo reagent

(3) Parallel assay of urinary extracts on the guinea pig ileum and on the anæsthetized cat s blood pressure gave the same value for the histamine content

The procedures mentioned in 2 and 3 were performed essentially as described by Kahlson *et al* (1958 a) They were done with urine samples showing normal histamine content and samples with a high histamine content during pregnancy as well as in the puerperium

Results

I *Urinary Histamine during Normal Pregnancy*

Normal values for the urinary excretion of free histamine were given by Duner and Pernow (1956) They found no difference between the sexes The normal value in 17 cases was 11 9 ± 0 8 μg/24 hrs (mean ± S E M) with a range from 6 1 to 19

We have examined the urinary output of free histamine in 12 healthy non pregnant women Urine was collected for at least two to three days and the mean value for each woman calculated The mean of these mean values was 12 5 ± 2 0 μg/24 hrs with a standard deviation of 6 9 As upper level of normal urinary excretion of free histamine we have therefore chosen somewhat arbitrarily a mean value for two or three observations above 30 μg/24 hrs (*i e* the normal mean + 2 5 × S D) This level should not be used for a rigid separation between normal and elevated histamine excretion in women, but rather as a means of classification in groups as in Tables II and IV Observations of changes in excretion in one and the same patient, *e g* after delivery provide supplementary information

The figures for urinary excretion of free histamine in Table I refer to women without toxæmia Most of them were entirely normal but as seen in Table I there were a few cases with

Table I *Urinary Excretion of Histamine in Normal Pregnancy (Urine Collected 1–15 Days before Delivery)*

Case No	Diagnosis	Duration of Pregnancy	Weight of Child (kg)	Urinary Histamine μg/24 Hours			No. of Observations
				Mean Value ± S E M	Highest Value	Lowest Value	
1	pruritus	normal	3 7	67± 4 1	82	42	9
2	normal	premature birth	2 4	22	24	19	2
3	»	normal? prolonged pregnancy?	4 4	8	10	6	3
4	»	prolonged pregnancy	4 0	180	—	—	1
5[a]	»	»	3 9	300± 54	590	160	9
6	»	normal	3 9	17± 3 5	31	9	0
7	cystitis	»	3 4	15± 5 3	50	5	7
8	normal	»	3 6	about 3	5	<1	8
9	»	»	3 8	15± 3 5	30	5	7
10	»	»	3 3	82	93	71	2
11	»	prolonged pregnancy	3 5	285±120	560	68	4
12[b]	»	normal	4 1	39± 3 1	63	25	11
13	»	»	3 6	38± 4 2	63	15	12
14	»	»	4 2	40± 2 9	46	30	5
15	»	»	4 4	9	10	7	2
16	»	»	3 9	12	16	7	3
17	hypertension	»	3 5	46± 3 8	77	24	13

a) Shown in Fig 2
b) " " " 1

abnormal duration of pregnancy and one case of hypertension without other signs of toxæmia This series of pregnant women is called normal merely to distinguish it from the series of toxæmic cases (Table III) It will be seen from Tables I and II that 9 of the 17 women had a mean urinary histamine level of more than 30 μg in 24 hours In these 9 cases, and in 3 others, a reduction of the urinary histamine occurred after delivery This may be taken as evidence that the urinary histamine level was elevated during pregnancy in 12 cases of the 17 studied

Table II *Survey of the Histamine Excretion in Normal Pregnancy (Data from Table I)*

	No. of Cases	Average Histamine Excretion before Delivery			Reduction after Delivery[1]
		< 30 µg/24 Hrs	30~100 µg/24 Hrs	> 100 µg/24 Hrs	
Normal duration	13	7	6	—	8
Premature birth	1	1	—	—	1
Prolonged pregnancy	3	—	—	3	3
Total	17	8	6	3	12

[1] Reduction after Delivery means that the basal level of histamine excretion was reduced after parturition The brief elevations of urinary histamine in the puerperium (see Fig 6) are thus ignored The figures denote the number of cases

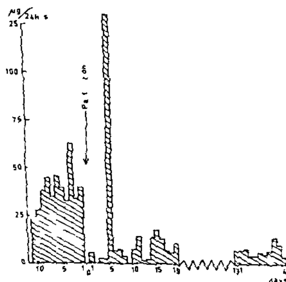


Fig 1 Urinary histamine in µg/24 hrs in a normal case (Case 12) Note elevated levels with reduction at delivery (day 0) except for day 5 The reduction was maintained during (days 2–19) and after the lactation period (days 131–141)

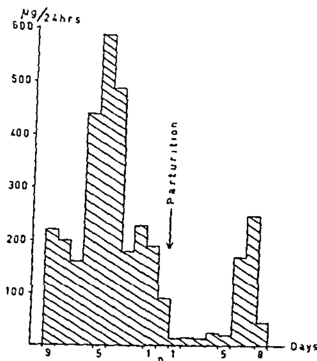


Fig 2 Urinary histamine in prolonged pregnancy (Case 5) Note high levels before delivery, with subsequent reduction except for days 6 and 7 Urinary culture on day 5 before delivery (day −5) No growth of bacteria

Fig 1 shows in detail the histamine excretion in one normal case It will be seen that the reduction at the time of delivery was maintained four months later, when the lactation was finished The brief elevation of urinary histamine on day 5 after delivery will be commented upon in section 3 below

There were 3 cases in which there was a certain diagnosis of

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a) Shown in Fig 3
b) 4
c) 5

[1] P E = pre-eclampsia
[2] Albuminuria without permanent hypertension
[3] Albuminuria and persistent diastolic hypertension
[4] Albuminuria persistent diastolic hypertension clinical judgement of imminent eclampsia
[5] Cases 34 and 35 had attacks of eclamptic convulsions shortly before and after delivery

Table [illegible] (Summary)

Case	Diagnosis	Duration of Pregnancy	Weight of Child (Kg.)	Highest Blood Pressure (mm Hg)	Albumin urea (‰)	Increase in Weight (Kg.)	Urinary Histamine µg/24 Hours: Mean ± S.E.M.	Highest Value	Lowest Value	No. of Observations
18	P.E.[1] mild[2]	Normal	3.1	140/105	2.0–4.0	16	52	58	46	2
19[a]			3.3	140/105	0.5–2.0	—	132 ± 25	250	43	9
20			2.[illegible]	—	0–1.3	10	49 ± 5.5	78	20	10
21			2.6	135/85	0.7–1.8	17	42 ± 15	95	16	5
22			4.1	160/100	1.0–1.8	9	67	71	63	2
23			3.4	135/100	1.0–5.0	17	16 ± 2.1	44	5	16
24	» »		3.2	145/110	0.5–1.0	16	7.5 ± 3.3	4[illegible]	<1	14
25	P.E. severe[4]	Short 19 days shorter than expected	2.1	140/110	7.0–10.0	13	16 ± 6.6	140	<1	23
26	P.E. moderate[3]	Normal	2.6	155/115	3.0–6.5	17	112 ± 39	780	11	20
27	»	»	2.5	150/100	0.5–2.5	11	97 ± 35	1100	12	32
28	P.E. severe	Short [illegible]0 days shorter than expected	2.7	175/115	0.7–4.7	[illegible]	6.7 ± 0.8	14	<3	13
29[b]	» »	Normal	3.0	160/110	4.0–6.0	17	16 ± 1.6	26	8	10
30[c]	P.E. moderate	Short 28 days shorter than expected	2.5	170/115	2.0–6.0	7	1200 ± 5[illegible]0	9300	13	16
31	»	Normal	2.6	145/100	1.0–2.0	13	35 ± 4.6	77	about 4	21
32	P.E. severe twins	»	2.5 2.5	180/140	0–1.0	13	126 ± 35	200	59	4
33	P.E. moderate	Short 15 days shorter than expected	2.5	160/105	0.8–4.5	15	19 ± 9.2	120	<2	13
34	Eclampsia[8] twins	Normal	3.1 2.5	170/120	1.0–4.7	18	about 3	7	<1	15
35	Eclampsia	Short 17 days shorter than expected	2.5	1[illegible]0/120	1.1	—	<[illegible]	—	—	1

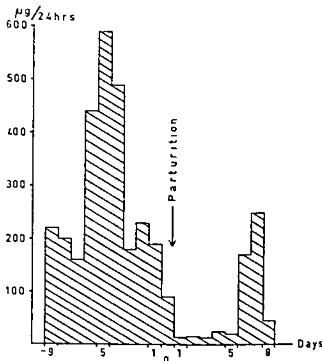


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Ta na

se	Diag is	Dur n of g st	W of kg	Blood pressure mm Hg	A u	Increase in W kg)	Urinary Histamine: M ± S E M	Max Value	Lowest Value	N of Obs v ns
			3	40 05	2 0 4 0	6	52	58	46	2
18	1 L ld	Nor al	3 3	140 105	0 5 2 0		132 ± 25	250	43	)
1			2	—	0 3	0	4) ± 5	75	20	10
20			2 6	35 85	0 7— 1 5	17	42 ± 15	95	16	5
21			4	160 00	1 0 8	9	67	71	63	2
22			3 4	135 100	1 0 5 0	17	18 + 2 1	44	5	16
23			3 2	145/110	0 5 1 0	18	7 5± 3 3	4)	<1	14
24										
25	1 E severe[a]	Sl rt 19 days sl orter tl a exp ct d	2 1	140/1 0	7 0—10 0	13	16 ± 6 6	140	<1	23
26	1 E mod rate[a]	Nor al	2 6	55 115	3 0 6 5	17	112 ± 39	780	11	20
27	"		2 5	150/100	0 5— 2 5	11	)7 ± 35	1100	12	32
28	1 E sev re	Sl ort 20 days sl orter a expected	2 7	1 5 115	0 7 4 7	)	6 ± 0 8	14	<3	13
2)[b]		Nor al	3 0	160 110	4 0 6 0	17	16 ± 1 6	26	6	10
30[c]	1 E od a e	S o t 28 days sl o ter tl a exp cted	2 5	170 115	2 0 6 0	7	00 ±590	9300	13	16
31	"	Nor al	2 6	145 100	1 0 2 0	13	35 ± 4 6	77	about 4	21
32	1 E severe tw s	"	2 8 2 5	180/140	0 — 0	13	126 ± 35	00	53	4
33	1 E oderate	Sl ort 15 days sl orter tl a exp t d	2 5	160 105	0 8 4 5	15	19 ± 7 2	120	<2	13
34	Ecla psia[a] t v s	Nor al	3 1 2 5	170 120	1 0 4 7	18	about 3	"	<1	15
35	Ecla p a	Sl o t 17 days sh rter tl a exp cted	2 5	1 0/120	1 1	—	<		—	1

post-maturity All these cases had a high histamine excretion, with reduction after delivery (Fig 2) The children of these patients were large In the whole normal series there was, however, no apparent correlation between the weight of the child at birth and the level of histamine in the mother's urine

There was no apparent correlation between the urinary histamine excretion and the age and previous obstetrical history of the patient Likewise, various therapeutic measures (e g medication with iron, vitamins and barbiturates) did not affect the urinary excretion of histamine

Great care was taken in collecting urine to avoid the possibility of formation or decomposition of histamine by bacteria As stated, after each voiding the urine was immediately put in a bottle with strong hydrochloric acid However, the possibility existed that bacterial growth in the urinary tract could be a cause of the high histamine excretion in pregnancy This possibility could be excluded in several cases, in which bacteriological culture of the urine was made in addition to the routine examination of the urinary sediment for bacteria (see Fig 2) Moreover, the prompt reduction of urinary histamine after parturition strongly suggests that the cause is not urinary infection, since the latter should not disappear so quickly

II *Urinary Histamine during Toxæmic Pregnancy*

The urinary excretion of histamine was studied in 18 cases with toxæmia of pregnancy (Tables III and IV) The classification of cases with pre-eclampsia is difficult The criteria used in the present study (see Table III) may be criticized, but it was considered necessary to have some sort of grouping, in order to correlate the histamine excretion with the severity of the toxæmic condition

It will be seen from Tables III and IV that among the 12 cases labelled mild or moderate pre-eclampsia there were 9 which had an urinary histamine level over 30 μg/24 hours In a 10th case there was a definite reduction after delivery so it can be said that 10 out of 12 patients in these groups had an elevated histamine excretion during pregnancy This should be compared

Table IV *Survey of the Urinary Excretion of Histamine in Toxæmia of Pregnancy (Data from Table III)*[1]

	No of Cases	Average Histamine Excretion before Delivery			Reduction after Delivery
		<30 μg./24 Hrs	30–100 μg./24 Hrs	>100 μg./24 Hrs	
Mild pre-eclampsia	7	2	4	1	6
Moderate pre-eclampsia	5	1	2	2	4
Severe pre-eclampsia	4	3	—	1	1
Eclampsia	2	2	—	—	—
Total	18	8	6	4	11

For explanations see Table II

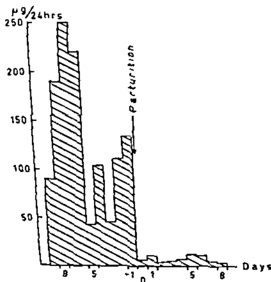


Fig 3 Urinary histamine in mild pre-eclampsia (Case 19) High levels before delivery A urinary culture was negative on day 6 before delivery

with the figures in non toxæmic cases (Table II) Such a comparison gives the impression that there is a larger number of cases with high urinary histamine in the groups of mild and

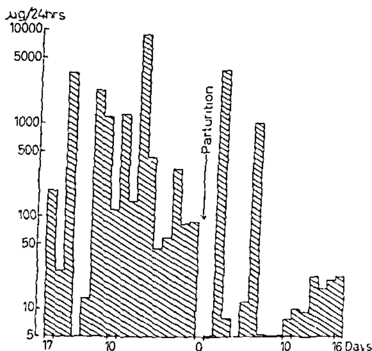


Fig 4 Urinary histamine in moderately severe pre-eclampsia (Case 30) Very high, irregular excretion of histamine Normal urinary sediment on days 17, 13, and 6 before delivery Urinary culture on day 4 (−4) before delivery no growth of bacteria

moderate pre eclampsia than in normal cases with normal duration of pregnancy

Fig 3 shows a mild case of pre eclampsia with high histamine excretion and prompt reduction at delivery and Fig 4 shows a case of moderately severe pre eclampsia with a histamine excretion which varied widely We could not find any clinical correlates to these variations in the urinary histamine

In the group with severe toxæmia and in the 2 cases of eclampsia, 6 cases in all, there was only one with high urinary histamine (Tables III and IV) In the 2 cases of eclampsia the urinary histamine was low, or undetectable, in several urine specimens Special care was taken to find out whether these urines contained agents which could interfere with the biological estimation of histamine This was not the case, however, since histamine added to such urine could be adequately recovered, as described in the methodological section

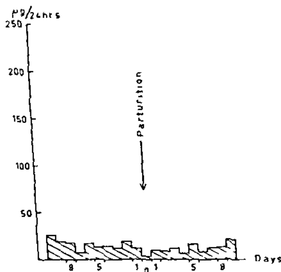


Fig 5 Urinary histamine in severe pre-eclampsia (Case 19) Normal histamine excretion before and after delivery

Fig 5 shows a case of severe pre eclamptic toxæmia in which the urinary histamine was low but possible to determine

Most of the patients with toxæmia received treatment with drugs such as diuretics and barbiturates but there was no apparent relation between therapeutic measures and urinary histamine

As in the normal group infections of the urinary tract could not explain the changes in histamine excretion observed in the group of toxæmic pregnancy (See Figs 3 and 4)

III *Urinary Histamine in the Puerperium after Normal or Toxæmic Pregnancy*

It can be seen from Figs 1 and 2 that the histamine excretion was promptly reduced after delivery but that a brief and pronounced increase occurred at about the 5th day When first seen this phenomenon was thought to be due to an error in the urine collection However a further analysis showed that this post partum peak value was common after normal pregnancy

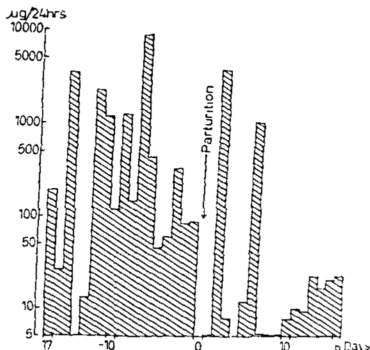


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case was a woman with mild pre eclampsia (Case 21, Table III) and the other case was one with moderate pre-eclampsia (Case 30, Table III and Fig 4)

As yet, no attempt has been made to find out whether the brief elevation of urinary histamine in the puerperium is accompanied by changes in the blood histamine level

The question of urinary infection as a cause of the post partum elevation of urinary histamine may be raised It was found that women could exhibit this elevation in urinary histamine also when bacteriological culture and urinary sediments showed that the urine was sterile This was particularly evident in Case 16 (Fig 6), in which a urinary culture was made on the very day an increase in histamine output was recorded

IV *Blood Histamine in Mothers and Children*

Observations on the histamine concentration in venous blood from the mother were made before and some days after delivery There was no significant difference between the blood histamine content in normal mothers and in mothers with toxæmia either before or after delivery *Table V shows the mean* values before delivery In the normal cases the blood histamine values were slightly higher in the puerperium than before delivery (mean increase 4 4 ± 2 6 μg/l, 5 cases) In the toxæmic cases the blood histamine tended to decrease after parturition (mean decrease 4 0 ± 4 0 μg/l, 10 cases) Neither change was statistically significant The cases with severe pre eclampsia or eclampsia had a slightly higher blood histamine level before

Table V *Mean Values for Blood Histamine (μg/liter Whole Blood)*

Mothers	Normal pregnancy	31 ± 4 7	8	
	Toxæmia	34 ± 5 2	13	
	At delivery	13 ± 1 3	10	(Table IV)
Children	Umbilical artery	87 ± 12	9	(Table V)
	Umbilical vein	69 ± 8 5	13	
	Difference artery—vein	13 4 ± 6 4	9	

The figures denote mean ± S E M and the number of observations

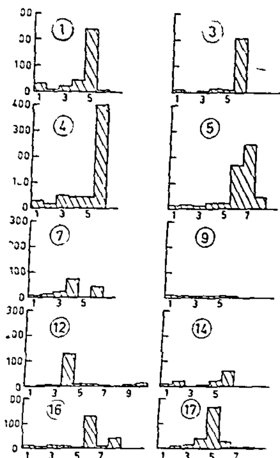


Fig 6 Urinary histamine in µg/24 hrs (same vertical scale for all diagrams) in the puerperium after normal pregnancy Ten cases from Table I are shown Encircled figures = case numbers The figures below the horizontal lines denote days after delivery, which took place at day 0

Of the 17 normal patients in Table I, 10 were studied for 6 days or more after parturition The values for urinary histamine in the puerperium of these cases are shown in Fig 6 It will be seen that only one case failed to show the post partum elevation of urinary histamine, which in the other cases occurred at the 4th to the 6th day

In the cases of toxaemia (Table III) this post partum elevation of urinary histamine occurred rarely (Figs 3 and 5) Of the 18 cases in Table III, 14 were studied for 6 days or more after delivery A post partum peak was seen in 2 cases only One

delivery (44 0 ± 15 5 μg/l, 4 cases) than those with mild or moderate pre eclampsia (30 1 ± 3 2 μg/l, 9 cases)

In the series of women with toxæmia and in the normal group there was no correlation between the urinary histamine and the blood histamine level A blood sample was obtained during eclamptic convulsions in one woman (Case 34, Tables III and VI) The blood histamine value was 12 μg/l, and the urinary histamine was about 2 μg./24 hours during that day

At the moment of delivery, and some hours before and after, low blood histamine values were obtained in whole blood from the mother (Tables V and VI) The decrease in blood histamine at parturition was statistically significant

Blood was taken from the umbilical vessels of the child at birth It was not always possible to obtain a clean and large enough sample from the umbilical artery It will be seen from Tables V and VI that the histamine levels were often quite high in umbilical cord blood especially if compared with the lowered level in the mother s blood In 7 out of 9 cases the histamine content was higher in blood from the umbilical artery than in blood from the vein Although the arterio-venous difference was quite large in 3 children it was not statistically significant for the whole series of 9 cases (p value about 0 07)

There was no correlation between the weight of the child and the blood histamine level in its umbilical vessels Neither was there in the few cases studied any apparent correlation between the urinary excretion of histamine of the mother before delivery, and the blood histamine level or the arterio venous histamine difference of the child at birth

Discussion

The observations presented would seem to allow the following conclusions

(1) The urinary excretion of histamine is moderately elevated in about half of normal pregnancies Prolonged pregnancy is associated with a more pronounced increase in the urinary histamine

(2) The histamine excretion in the urine is often high or

Table VI *Histamine Concentration (μg per Liter) in Whole Blood from the Umbilical Vessels and from the Mother's Cubital Vein (Blood Samples at Parturition Taken Simultaneously from Mother and Child)*

Case No[1]	Diagnosis	Child Sex and Weight (kg)	Histamine Concentrations							
			Umbilical		Difference	Maternal Venous Blood				
						Before Delivery (During Labour)		At Delivery	After Delivery	
			Artery	Vein	Artery – Vein	15 – 1 Days	24 – 0 Hrs		0 – 24 Hrs	1 – 7 Days
51	Normal	F[2] 3 7	111	125	– 14	—	13	13	12	—
52	»	F 2 9	114	109	5	—	10	—	16	—
53	Fœtal asphyxia	F 3 5	93	83	10	–	–	11	6	—
54	Normal	F 2 8	40	33	7	—	33	17	18	—
55	»	M[3] 3 2	135	100	35	—	9	6	5	—
9		F 3 8		108	—	42	–	15	—	50
4	Post-mature	M 4 0	54	49	5	—	13	—	–	33
5	»	F 3 9	114	69	45	22	27	18	20	32
19	Pre-eclampsia	M 3 3	46	48	2	38	14	14	13	31
26	»	M 2 6	—	36	—	20	20	17	–	18
27		M 2 5	72	42	30	26	15	8	10	20
34	Eclampsia twins	M 3 1		55	—					
		F 2 5	—	50	–	14	12[4]	12	—	20

[1] Case numbers below 35 refer to the same patients as shown in Tables I and III

[2] F female

[3] M male

[4] Taken during eclamptic convulsions

(a) increased intake, (b) decreased inactivation, (c) increased liberation, and (d) increased production

Of these possibilities, (a) may be excluded with reasonable certainty, since many of these patients with different urinary histamine levels were studied simultaneously in the same wards and given the same food Increased intake of histamine formed by bacteria in the intestines must also be considered The instantaneous reduction of urinary histamine at delivery is against this possibility

With regard to (b), it can be argued that many observations favour the assumption that histamine inactivation is, if anything, increased during normal pregnancy (cf Nilsson *et al*, 1959) A decrease in serum histaminase activity has admittedly been found in toxæmia (Kapeller-Adler, 1949, and others), but these findings have not been confirmed by Swedish workers using another method (Ahlmark and Werko, 1950, Swanberg 1950) Moreover the most pronounced reductions in histaminase activity have been seen in severe pre eclampsia, and in these cases the urinary histamine was mostly normal or low

Regarding (c) it can be said that if increased liberation of histamine occurs, there must be a concomitant increase in the rate of its production since the increase in urinary histamine *during pregnancy was often steady and prolonged*

The balance of the evidence, in our opinion suggests that increased formation of histamine takes place during pregnancy in man as it does in the rat (Kahlson *et al* 1958 b) The place(s) and the cause(s) of the increased production are at present unknown It is possible that the human kidney, like that of the dog (Lindell and Schayer, 1958) can decarboxylate histidine to histamine and excrete this directly into the urine The possibility that such a mechanism might lie behind the increased urinary histamine during pregnancy is to some extent supported by the observations that there was no correlation between the blood histamine concentration and the urinary histamine and that women with a high urinary histamine exhibited none of the signs usually seen during an intravenous infusion of histamine On the other hand it has repeatedly been shown that an intravenous infusion of histamine which is large

very high in mild and moderately severe pre eclamptic toxæmia In severe pre-eclampsia or eclampsia the urinary histamine level is low

(3) The blood histamine values of the mothers are not correlated with their urinary excretion of histamine The new born child has a high blood histamine level and there is some evidence of an arterio-venous difference in histamine concentration in the umbilical vessels

(4) After a normal pregnancy there is often a brief but pronounced elevation of the urinary histamine at the 4th to the 6th day after delivery This elevation is only rarely seen after toxæmic pregnancy

These points will now be discussed and related to previous work As to the urinary histamine, the present observations confirm to some extent the early work of Kapeller-Adler and Adler (1943) After precipitation and extraction, they could obtain a crystalline compound from the urine when adding flavianic acid The crystals had many properties in common with histamine diflavianate Urine from patients with normal pregnancy yielded non-measurable amounts of histamine diflavianate, but in cases of hyperemesis gravidarum and mild pre eclampsia quite substantial amounts were found The amounts found were of the same order of magnitude as those found in some cases in the present study Kapeller-Adler and Adler also found the histamine output to be low or unmeasurable in severe pre eclampsia or eclampsia The sensitivity of their method was much lower than that of the biological methods now available, and this necessitated pooling of the urine from several days Therefore they were not able to study the more discrete changes in urinary histamine in normal pregnancy and the puerperium, or the rapid changes at delivery disclosed in the present study Their work also presents additional biochemical evidence of the identity with histamine of the gut contracting substance found in urines from patients with mild pre eclamptic toxæmia

The present study has demonstrated that the free histamine present in the urine in many pregnant women is not formed by bacteria What is the cause of the increased histamine excretion? The following possible explanations will be considered

vessels do not present a clear picture, but they offer some support for the view that histamine formation takes place in the human fœtus The problem is, however, far from being solved, since it has been found that human fœtal tissue does not produce histamine *in vitro* (Kahlson *et al*, 1959) In rat fœtal tissue histamine formation was very rapid *in vitro* (Kahlson *et al*, 1958 b) However, the failure to demonstrate histamine formation *in vitro* by human fœtal tissues cannot be taken as definite evidence that the process does not occur *in vivo* Histamine formation is very difficult to demonstrate in human tissues (Lindell and Westling, unpublished) in comparison with rat tissues

Even if the theory of histamine production by the fœtus is accepted there is clearly still much work needed to clarify the role of histamine in human pregnancy It will be necessary to find out whether changes in the rate of production and/or the rate of catabolism of the formed histamine can account for the differences observed in the urinary histamine in different patients and in different abnormalities of pregnancy As regards toxæmia of pregnancy the evidence seems rather to be against histamine as a causative factor (Kapeller-Adler, 1949) since the more severe cases have a low urinary histamine A disturbed renal function could theoretically be responsible for the low excretion of histamine in severe toxæmia but this cannot be so in our two cases of eclampsia, because their serum creatinine level was not elevated Moreover, the blood histamine was found to be low during an attack of eclampsia, and there is thus no support for a theory of histamine retention due to renal failure

The low histamine concentration in the mother's blood at parturition seen in the present study was described by Marcou Athanasiu Vergu Chiriceanu Cosma, Gingold and Parhon (1938) and others The low blood histamine may be due to an increased secretion of adrenocortical hormones since cortisone reduces blood histamine in children (Mitchell and Cass 1959) A similar effect has been seen in pregnant women during therapy with hypophyseal adrenocorticothrophic hormone (unpublished observation)

An intriguing phenomenon is the brief elevation of the urinary

enough to cause subjective symptoms and a rapid gastric acid secretion, will not give rise to a measurable increase in the plasma histamine, but will lead to an increase in the urinary output of histamine (Adam, Card, Riddell, Roberts, and Strong, 1954) The lack of relation between blood and urinary histamine in the present study is therefore no proof that the urinary histamine is formed in the kidney

As mentioned earlier, recent work has revealed that the rat fœtus produces large amounts of histamine, which appear in the mother's urine (Kahlson *et al*, 1958 b) There is in fact some evidence, apart from that provided by analogy, which suggests that the human fœtus may also be a source of histamine First, the urinary excretion of histamine is promptly reduced at delivery Second, the child's blood is relatively rich in histamine at birth (Wicksell, 1949 b, Mitchell and Cass, 1959) and in the present study there was a tendency for the histamine level to be higher in the umbilical artery than in the vein Such an arterio-venous difference could be due to removal of histamine in the placenta

The concentration of histamine in the plasma from the umbilical vessels at birth was investigated by Wicksell (1949 b) He found no difference between the plasma level of histamine in the umbilical artery, the umbilical vein and in venous blood from the mother On the other hand, Pettay (1950) found quite high plasma histamine levels in umbilical cord blood', levels that were higher than those in adults The findings of Pettay were criticized by Mitchell and Cass (1959) who found that the plasma histamine level in the umbilical vein at birth was so low that it could not be measured, just as it is in adults (Adam, Hardwick and Spencer 1957) However Kahlson, Rosengren, and White (1959) have recently confirmed that plasma from fœtal arterial blood mostly contains histamine in measurable amounts while the plasma histamine in the mother was not detectable Further, they found that the umbilical vein plasma contained less histamine than that in the artery which again points to the possibility of removal of histamine during the passage through the placenta

The studies on blood and plasma histamine in the umbilical

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histamine in the puerperium, commonly seen after normal pregnancy but only rarely after toxæmia This post partum peak value had no apparent relation to the mode of delivery of the patient or to external events such as medication, and enemata. The only woman with normal pregnancy who did not show the 'peak value', did not want to nurse her child and was given œstrogens to suppress lactation There were however some patients with pre-eclampsia who had good milk production and still did not exhibit the elevation of urinary histamine in the puerperium Further work is needed to elucidate the cause of the post partum elevation of urinary histamine

SUMMARY

In 12 out of 17 pregnant women, without signs of toxæmia, the urinary excretion of free histamine was increased before delivery, with a prompt reduction after it The increase was moderate except for 3 cases of prolonged pregnancy which had a higher urinary histamine than the others

In mild or moderately severe pre eclamptic toxæmia the urinary histamine was increased, sometimes up to very high values

In severe pre eclampsia and eclampsia the urinary histamine was generally low

There was no correlation between the blood histamine values and the urinary excretion of histamine

At the moment of birth, the mother's blood histamine content was lowered *Blood from the child had a high histamine concentration* Blood from the umbilical artery often contained more histamine than blood from the umbilical vein

A brief but pronounced increase in the urinary histamine was seen at the 4th to the 6th day after delivery in patients with normal pregnancy This increase after delivery was rare in patients with toxæmia of pregnancy

The causes of the increased urinary excretion of histamine during pregnancy and after delivery are at present unknown Increased urinary histamine during pregnancy may be caused by histamine formation in the fœtus

albumen which has less affinity for hydrocortisone but possesses a higher total capacity than does transcortin (Sandberg and Slaunwhite, 1959, Daughaday, 1958 b)

The present study was carried out to investigate whether a relationship exists between the hydrocortisone level and the plasma protein level in cord blood and in maternal blood

Present Investigations

Method and Material

Fractionation of serum proteins by paper electrophoresis was carried out as described by Uhrbrand (1958) Total protein was determined by the biuret test

Plasma hydrocortisone was determined by the method of Bojesen (1956) which unlike previous methods, is specific for hydrocortisone [1]

All analyses were carried out in duplicate

The patients were women admitted either because of spontaneous abortion (16 cases) or for Cæsarean section (2 cases)

The first 7 patients received a single dose of hydrocortison,[2] 200 mg in 500 l isotonic glucose administered intravenously twenty to hundred and five minutes before abortion occurred or Cæsarean section was performed The next 11 received an initial dose of 100 mg hydrocortisone in 250 ml isotonic glucose, followed by continuous drip of a solution of the same strength, 60 drops per minute, in order to maintain the plasma level constant

In the 7 cases given a single dose, a blood sample for hydrocortisone determination was drawn at the same time from the umbilical vein and from the mother s cubital vein In collecting the cord blood admixture of maternal retroplacental blood was avoided In the 11 cases where the mother received a continuous infusion maternal blood was collected twenty to thirty minutes after administration of the initial dose and again at abortion in order to ascertain whether or not the plasma level had remained

[1] Analyses were performed at Medicinsk Laboratorium Copenhagen
[2] Hydrocortisone Leo Infusion Concentrate

Leyssac P Acta obst. et gynec Scandinav 4 174, 1961

From the Copenhagen County Hospital, Department of Gynæcology G (Vald Madsen, M D) and the Central Laboratory (G C Brun, M D) Gentofte, Denmark

HYDROCORTISONE IN FŒTAL PLASMA FOLLOWING INTRAVENOUS ADMINISTRATION OF HYDROCORTISONE TO THE MOTHER

Part I With Special Reference to the Binding of Hydrocortisone by Plasma Proteins

BY

P LEYSSAC

Recent investigations into the fate of hydrocortisone in the body and its binding to plasma proteins are of interest in evaluating the transport of steroids through the placenta

Hydrocortisone will readily pass through the placenta, even in the high concentrations obtained following intravenous infusion of hydrocortisone to the mother (Migeon *et al*, 1956, 1957) Nevertheless, the concentration of 17 hydrocorticosteroid in the cord blood is lower than in the maternal blood This generally applies also to physiological, endogenous concentrations (Gemzell, 1954, Migeon *et al*, 1955, Kawahara, 1958)

Hydrocortisone is bound to plasma protein in a reversible binding (Eik-Nes *et al*, 1954) At low concentrations, below about 15 μg per 100 ml , this binding is very strong (Daughaday 1958 a, Upton and Bondy 1958) and occurs bound to a globulin, transcortin (Daughaday 1958 b, Slaunwhite and Sandberg, 1959) At higher concentrations of hydrocortisone the transcortin becomes saturated after which hydrocortisone is bound to an increasing extent by other proteins, especially by

albumen which has less affinity for hydrocortisone but possesses a higher total capacity than does transcortin (Sandberg and Slaunwhite, 1959, Daughaday, 1958 b)

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constant At the time of abortion, blood was drawn from the umbilical vein as in the first experiments

In practically all the experiments, the maternal concentration remained constant or increased slightly

In 6 out of the 18 experiments, venous blood from the mother and cord blood was collected at abortion for serum electrophoresis and protein determination In 3 cases where the fœtus was too small to permit collection of sufficient blood for hydrocortisone analysis, specimens of maternal and cord blood were obtained for protein determination

A total of 18 mothers received hydrocortisone. They were delivered of 19 fœtuses of an average maturity of 5 5 months (4–8 months) The 9 fœtuses whose blood was studied by serum electrophoresis, were also of an average maturity of 5 5 months (3 1/2–7 months)

Results

Table I gives the umbilical/maternal ratio of the plasma protein fractions in 9 fœtuses and their mothers These values are mean values calculated from the ratio in each pair separately The ratio was calculated for the relative values, *i e* in per cent of total protein as well as for the absolute values in g per 100 ml plasma

As is evident from Table I there is a relative excess of albumin in the fœtus, an almost equal percentage of α_1 in the fœtus and its mother but a preponderance of the other fractions in the

Table I *Plasma Proteins in the 5th–6th Months of Gestation Umbilical/Maternal Ratio*

	Relative	Absolute
Total protein		0 60
Albumin	1 31	0 80
α_1	1 14	0 69
α	0 62	0.36
β	0 59	0 33
γ	0 52	0 42

maternal blood As far as the absolute values are concerned, on the other hand, the fœtus showed lower values of total protein as well as of all protein fractions, the fœtal concentration of total protein was only 60 per cent of the maternal level

Table II shows the hydrocortisone levels in the maternal and fœtal blood in the 18 experiments and the calculated umbilical/maternal ratio The mean value of the ratio was calculated, and e^M stands for the statistical mean error As is apparent from the figures the difference between maternal and umbilical concentrations was significant, the t value being 7 9

Tables I and II show that the umbilical/maternal ratio of total protein corresponds to the ratio of hydrocortisone in the plasma

Table II Concentration of Hydrocortisone in Maternal and Fœtal Plasma after Intravenous Infusion of Hydrocortisone to the Mother in the 5th–6th Month of Gestation

N	Age	Maternal	Umbilical	Umbilical/Maternal Ratio
1	5 months	127 microg %	80 microg %	0 63
2	5	276	185	0 67
3	7	234	144	0 62
4	8	240	166	0 69
5	5	227	163	0 72
6	4	133	81	0 61
7	4	187	111	0 59
8	8	157	117	0 74
9	5	204	105	0 51
			95	0 47
10	5	255	98	0 38
11	5	164	143	0 82
12	6	251	85	0 34
13	6	249	124	0 50
17	5	202	81	0 39
18	6	264	156	0 59
19	4	291	189	0 65
21	6	140	102	0 72
22	6	169	69	0 41
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Average maturity 5 1/2 months

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Average maturity 5 1/2 months.

Discussion

Considering that hydrocortisone is present in a reversible binding to plasma protein and that the freely diffusible fraction of hydrocortisone readily passes the placenta, the theoretical expectation was a diffusion equilibrium adjusting itself between the diffusible fractions in the fœtal and maternal blood and a binding of hydrocortisone in a quantity corresponding to the fœtal plasma protein level

It is not likely that the low hydrocortisone levels in the cord blood, compared with those in maternal blood, are due to the time from the administration of the initial dose until the sampling having been too short for the adjustment of an equilibrium The fact is that the same difference was demonstrable whether the sample was drawn twenty or hundred and five minutes after the administration of a single dose or after continuous infusion for up to 4 hours during which the maternal level remained constant

On the other hand, it may be that the fœtus can eliminate hydrocortisone so rapidly as to show a very low concentration in the umbilical artery, this might then be the reason why an equilibrium could not be attained during the passage of the blood through the placenta Kawahara (1958) found a very low concentration of 17-hydroxycorticosteroids in blood samples from the umbilical artery obtained following normal vaginal delivery, while blood drawn at the same time from the umbilical vein showed materially higher levels Similarly, Leyssac (1961) has demonstrated that hydrocortisone is rapidly eliminated from the fœtal blood during its passage through the fœtal liver, as the hydrocortisone level in blood from the left heart was lower than that in blood collected almost simultaneously from the umbilical vein However, a rapid elimination of hydrocortisone from the fœtal blood cannot explain levels in the umbilical vein lower than in the maternal blood The fact is that in 2 experiments, where the fœtuses were anoxic and the concentrations in the cardiac blood – presumably for that reason – were of the same level as in the umbilical vein, the concentrations in the umbilical

vein were nevertheless lower than in the maternal blood In these 2 cases, elimination cannot have taken place

The conformity between the proportionate levels of hydrocortisone and plasma protein are in keeping with the hypothesis advanced A statistical correlation is not directly demonstrable in the 6 experiments in which hydrocortisone analysis as well as protein determination were carried out on corresponding blood samples from mother and fœtus, but this could not be expected as the protein concentrations in 5 to 6 month old fœtuses are in such a limited range that plotting of the protein ratio against the hydrocortisone ratio in a diagram will not give sufficient scatter of the values to draw a regression line It was impossible to procure a series of fœtuses with sufficient variation in the protein level for a statistical analysis

However none of the findings militates against the hypothesis that the lower concentrations of hydrocortisone in cord blood than in maternal blood are due to the binding of hydrocortisone by protein

Experiments showing that a diffusion equilibrium is obtained between the diffusible fractions of hydrocortisone in the fœtal and maternal blood would confirm the hypothesis

SUMMARY

Hydrocortisone was administered by infusion to pregnant women immediately before spontaneous abortion or Cæsarean section In their 19 fœtuses, of an average maturity of 5 5 months, the umbilical/maternal ratio of hydrocortisone in the plasma was 0 59 In 9 fœtuses also of an average maturity of 5 5 months and their mothers the average umbilical/maternal ratio of total protein was 0 60 Such close conformity was not demonstrable in the individual experiments, but is only apparent from the mean values The series does not permit a statistical assessment of any correlation between the concentration of hydrocortisone and that of plasma protein, since the fœtal protein concentrations are restricted to a too limited range

The author advances the hypothesis that the reversible binding of hydrocortisone by plasma protein accounts for the low concentrations in cord blood compared with those in the maternal blood

Acknowledgement

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HYDROCORTISONE IN FŒTAL PLASMA FOLLOWING INTRAVENOUS ADMINISTRATION OF HYDRO-CORTISONE TO THE MOTHER

Part II With Special Reference to Fœtal Elimination of Hydrocortisone

BY

P LEYSSAC

Intensive research into the intermediary metabolism of the corticosteroids has thrown new light upon a number of problems of theoretical as well as clinical interest

Hydrocortisone is eliminated by a number of enzymatic reduction processes The first step in this elimination is reduction to dihydrocortisone which takes place in the liver and which controls the rate of turnover Thereupon, reduction takes place to tetrahydrocortisone (Peterson *et al* 1955) The rate of elimination is proportional to the concentration in the plasma When cortisone is administered it is rapidly transformed into hydrocortisone, and the greater part of the biological activity of cortisone is ascribed to this hydrocortisone (Peterson *et al* 1957)

Full term fœtuses can also transform hydrocortisone Following infusion of C^{14} hydrocortisone to the mother *prior* to delivery, Migeon *et al* (1957) found the radioactivity in the cord blood to be $^{1}/_{12}$–$^{1}/_{5}$ of that in the maternal blood Twenty four to fourty eight hours after the infusion to the mother radioactivity was no longer demonstrable in the infant Migeon *et al* conclude therefore that the newborn *infant* is able to eliminate

hydrocortisone This assumption is supported by Kawahara's (1958) studies on the concentration of 17-hydrocorticosteroid in blood collected separately from the umbilical artery and the umbilical vein In normal, vaginal deliveries, the concentration in the artery proved low compared with that in the vein

According to the present findings, the fœtus is also able to eliminate hydrocortisone at an earlier stage of gestation

Method and Material

Plasma hydrocortisone was determined by the method of Bojesen (1956) This method is specific for hydrocortisone, unlike previous methods which determined the total amount of free 17 hydroxycorticosteroids All analyses were carried out in duplicate [1]

The series comprised 6 pregnant patients, admitted with incipient, spontaneous abortion towards the end of the 5th or the beginning of the 6th month of pregnancy

An initial dose of 100 mg hydrocortisone[2] in 250 ml isotonic glucose was administered to the mother in the form of an intravenous infusion from 30 to 120 minutes (average 74 minutes) before expulsion of the fœtus After the initial infusion, a continuous infusion of the same strength was maintained (60 drops/min) to keep the maternal plasma level constant To check the maternal hydrocortisone level, two blood samples were collected, one twenty to thirty minutes after administration of the initial dose and the other at abortion In all cases the maternal level remained constant or increased slightly When the fœtus had been expelled, the cord was cut and the fœtal stump clamped with a Pean forceps The placental end of the cord was emptied of venous blood, avoiding any admixture of maternal, retroplacental blood Simultaneously with the collection of cord blood, the fœtal chest was opened, and with a venous needle mounted on a heparinized syringe the fœtal heart was punctured either in the left atrium or the left ventricle, while the cardiac muscle was still moving in rhythmic contractions By this means, 3-10 ml of blood was

[1] Analyses were performed by Medicinsk Laboratorium Copenhagen

[2] Hydrocortisone Leo Infusion Concentrate

Table I *Concentration of Hydrocortisone in Maternal Plasma, Umbilical Vein Plasma and Plasma from Fœtal Heart after Infusion of Hydrocortisone to the Mother*

Experiment No.	Maternal Plasma microg. per 100 ml.	Umbilical Vein Plasma microg. per 100 ml.	Fœtal Heart Plasma microg. per 100 ml.
11	164	143	71
12	251	85	73
19	291	189	144
21	140	102	45
17	202	81	86
22	169	69	62

collected, and the entire procedure was completed within three minutes of the delivery

Results

The Table shows the hydrocortisone levels in the blood samples drawn simultaneously from the mother, from the cord, and from the left heart of the fœtus

It will be seen that the level in the fœtal heart was significantly lower than that in the cord blood in four of the experiments In two (Experiments 17 and 22) the levels in the cardiac blood and in the cord blood are the same These two abortions had been extremely difficult Case 17 had been in labour for more than two hours before expulsion of the fœtus which was flabby and showed signs of hypoxia In Case 22 the abortion was also prolonged and strenuous moreover the cord was wound twice around the neck, and the fœtus was severely anoxic and flabby

The course of the remaining abortions was uncomplicated

Lastly it may be emphasized that in all experiments the concentration in the cord blood was considerably lower than the maternal concentration regardless of whether or not the concentration in the cardiac blood was the same as that in the cord blood

Discussion

The finding that the concentration of hydrocortisone in the mixed fœtal cardiac blood was lower than in the cord blood cannot

be explained by rapid distribution to the extra-vascular fluid of the fœtus, since it must be considered to have become saturated during the continuous infusion to the mother before the abortion Consequently, the fall in concentration between umbilical vein blood and blood in the left fœtal heart must be due to elimination during the passage through the fœtal liver It is striking that the decrease could be so marked with the maximum period of two or three minutes elapsing from the cord being cut until the cardiac blood samples were collected During this interval, the blood could not have passed the liver more than a few times Although the values found do not permit a calculation of the half-life of hydrocortisone in the fœtus, it must be deduced that it is considerably shorter in the fœtus than in its mother Peterson *et al* (1955) found a half-life of hydrocortisone of about 115 minutes in adults Migeon *et al* (1957) reported that the half life is twice as long in pregnant as in normal non-pregnant women owing to a reduced rate of turnover towards the end of gestation The high rate of elimination in fœtuses in the present study is in striking contrast to the studies of Bongiovanni *et al* (1958) who found the half-life to be considerably prolonged, on the average nine hundred and seventy-seven minutes, in newborn infants following administration of hydrocortisone in the form of hemisuccinate On the other hand, the low concentrations of 17 hydroxycorticosteroid in the umbilical artery as compared with those in the umbilical vein in Kawahara s (1958) series are in keeping with the short half-life in the present study

A rapid elimination of hydrocortisone in the fœtus, as shown by the present study, must presumably be attributed to the relatively large fœtal liver

In 9 out of 47 experiments, Gemzell (1954) found a higher endogenous concentration of 17-hydroxycorticosteroid in the cord blood than in the corresponding maternal blood In two of these experiments the fœtuses had been delivered by forceps and were anoxic In Gemzell s opinion, the high concentration in the cord blood is due to the fœtal adrenal activity in response to the increased stress This presumption might be supported by the results of Kawahara (1958) after forceps delivery he found the concentration in the umbilical artery to be higher than following

normal delivery and as high as in the umbilical vein In two of the present experiments, there was no difference between the concentration of hydrocortisone in the blood from the umbilical vein and in blood from the left fœtal heart Both fœtuses were anoxic Two explanations may be imagined either the fœtal adrenal cortex can secrete hydrocortisone in response to stress or else the high concentrations in the cardiac blood and in the blood from the umbilical artery are due to a greatly reduced turnover in the fœtal liver when it is damaged by anoxia Recent animal experiments concerning the fœtal pituitary adrenal activity are highly in favour of the view of propounding an active interplay even in ante natal life It has not yet been shown clearly, however, whether the fœtal adrenals are in fact capable of producing hydrocortisone

Gemzell s claim that the concentration of hydrocortisone in the cord blood reflects fœtal adrenal activity cannot hold, however since the higher concentrations in the blood from the umbilical vein than in blood from the umbilical artery or mixed cardiac blood in normal deliveries, can be explained only by the transplacental passage of hydrocortisone from the maternal to the fœtal organism

Summary and Conclusions

Following continuous infusion of hydrocortisone to pregnant women prior to spontaneous abortion the plasma level of hydrocortisone was analysed in blood specimens drawn at practically the same time from the mother the umbilical vein and the left heart of the fœtus The concentration in the cardiac blood proved to be significantly lower than that in the umbilical vein blood in four experiments It is concluded that the fœtus is able to eliminate hydrocortisone at a metabolic rate more rapid than in adults

In two experiments where the fœtuses were anoxic the hydrocortisone level in the mixed cardiac blood was as high as that in the umbilical vein Whether the relatively high concentration in the cardiac blood was due to active secretion of hydrocortisone in the fœtus or to a reduced turnover in the fœtal liver damaged by anoxia is discussed

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Following continuous infusion of hydrocortisone to pregnant women prior to spontaneous abortion the plasma level of hydro cortisone was analysed in blood specimens drawn at practically the same time from the mother the umbilical vein and the left heart of the fœtus The concentration in the cardiac blood proved to be significantly lower than that in the umbilical vein blood in four experiments It is concluded that the fœtus is able to eliminate hydrocortisone at a metabolic rate more rapid than in adults

In two experiments where the fœtuses were anoxic the hydrocortisone level in the mixed cardiac blood was as high as that in the umbilical vein Whether the relatively high concentration in the cardiac blood was due to active secretion of hydrocortisone in the fœtus or to a reduced turnover in the fœtal liver damaged by anoxia is discussed

be explained by rapid distribution to the extra vascular fluid of the fœtus, since it must be considered to have become saturated during the continuous infusion to the mother before the abortion Consequently, the fall in concentration between umbilical vein blood and blood in the left fœtal heart must be due to elimination during the passage through the fœtal liver It is striking that the decrease could be so marked with the maximum period of two or three minutes elapsing from the cord being cut until the cardiac blood samples were collected During this interval, the blood could not have passed the liver more than a few times Although the values found do not permit a calculation of the half life of hydrocortisone in the fœtus, it must be deduced that it is considerably shorter in the fœtus than in its mother Peterson *et al* (1955) found a half-life of hydrocortisone of about 115 minutes in adults Migeon *et al* (1957) reported that the half life is twice as long in pregnant as in normal non pregnant women owing to a reduced rate of turnover towards the end of gestation The high rate of elimination in fœtuses in the present study is in striking contrast to the studies of Bongiovanni *et al* (1958) who found the half life to be considerably prolonged, on the average nine hundred and seventy-seven minutes, in newborn infants following administration of hydrocortisone in the form of hemisuccinate On the other hand, the low concentrations of 17 hydroxycorticosteroid in the umbilical artery as compared with those in the umbilical vein in Kawahara's (1958) series are in keeping with the short half life in the present study

A rapid elimination of hydrocortisone in the fœtus, as shown by the present study, must presumably be attributed to the relatively large fœtal liver

In 9 out of 47 experiments, Gemzell (1954) found a higher endogenous concentration of 17-hydroxycorticosteroid in the cord blood than in the corresponding maternal blood In two of these experiments the fœtuses had been delivered by forceps and were anoxic In Gemzell s opinion, the high concentration in the cord blood is due to the fœtal adrenal activity in response to the increased stress This presumption might be supported by the results of Kawahara (1958) after forceps delivery he found the concentration in the umbilical artery to be higher than following

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PYOGENIC INFECTIONS IN INFANTS

A Study Based on Health Visitors Records

BY

P HELMS and A. STENDERUP

The occurrence of superficial infections in infants has been studied particularly in maternity units, from which numerous reports have been published during recent years (Williams, Blowers Garrod and Shooter 1960) These studies have usually been prompted by epidemics of clinical infections principally due to Staphylococcus aureus As the studies revealed that a large number of the infants including many without manifest infections were on discharge nasal or skin carriers of Staphylococcus aureus several of the investigators emphasised that such epidemics involve the risk of spread of virulent staphylococci in the population

On the other hand fewer studies are available on the *endemic* occurrence of infections in maternity wards and in private homes

In order to gain an impression of such infections we have reviewed the records made out by the Public Health Nurses visiting the homes in the city and county of Aarhus (population approximately 210 000) during the two years 1956 and 1957 These records proved to contain sufficiently detailed and uniform information of eye and skin *infections in infants – infections* of the same type as those described in staphylococcal epidemics Our evaluation of the diseases described is based on the clinical data contained in the records since bacteriological studies for a detailed diagnosis were not available

The higher concentrations of hydrocortisone in the blood from the umbilical vein than in the mixed cardiac blood and the high concentrations in the fœtal blood following exogenous administration of hydrocortisone to the mother indicate that under the given experimental conditions the concentration of hydrocortisone in the umbilical vein blood is derived from the mother by trans placental passage

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A survey of the series and the frequency of infections is given in Table I It is seen that about 14 per cent of the infants had clinical infections within the first two months of life

The types of infection are listed in Table II, which shows that purulent conjunctivitis occurred as the only manifestation in 5 5 per cent and in association with skin infections in another 0 8 per cent Conjunctival irritation of short duration within the first few days of life, which might be referable to instillation of silver nitrate solution, was not recorded as conjunctivitis

Table II *Absolute and Relative Frequencies of the Individual Infections*

	No. of Cases		
Purulent conjunctivitis	352	5 5	
Typical pemphigus	254	4 0	512 = 8 0 %
Pemphigoid skin infection	205	3 2	
Typical pemphigus and purulent conjunctivitis	28	0 4	
Pemphigoid skin infect and purulent conjunctivitis	25	0 4	
Abscess and whitlow	50	0.8	
Pneumonia and otitis media	6	0 1	
Total	920	14 4	

Napkin area dermatitis – whether pustular or not – was not included in the material

Typical pemphigus was recorded in 282 cases including 28 associated with purulent conjunctivitis viz 141 cases in 1956 and 141 in 1957 For a diagnosis of pemphigus it was required either that this term was expressly used, or that the record contained a description of the presence of several concurrent purulent blisters It was difficult to differentiate this group from pemphigoid infections In view of the fact that the observations recorded were made by 36 different Health Visitors this differentiation is not an absolute one The two groups were therefore combined so that skin infections alone and skin infections complicated by purulent conjunctivitis were considered as one group under the designation skin infections which comprised a total of 512 cases or 8 0 per cent of all the infants considered

Of the total series 33 per cent were under medical care before

The Health Visitor pays her first visit to the home when the infant is about one week old, the visits are repeated each week during the first month and then at intervals of gradually increasing length Routine measurements and other observations are recorded at each visit The supervision is continued for twelve months, and at the end of this period the record is submitted to the National Health Service

Present Investigation

Our studies covered the period from the Health Visitor s first call until the infant had attained the age of two months

All records were reviewed in order to obtain information as to the following infections purulent conjunctivitis, typical pemphigus, pemphigoid skin infection, abscess, whitlow, and more severe infections, such as pneumonia and otitis media

The infections were recorded on punch cards together with information on the age of the infant at the development of the infection, therapeutic measures taken, birth weight, weight at one month, breast or artificial feeding and place of birth (at home, the State Maternity Hospital for Jutland, Private Maternity Homes or General Hospitals)

About 7,000 records were available for the two years, but some had to be excluded for various reasons (removal, supervision refused, transfer to infant homes, etc) Our total series comprises the remaining 6,383 records which had been kept from the birth of the infant till after the age of two months

Table I *Survey of the Series of Records from the City and County of Aarhus (1956 and 1957) and of the Absolute and Relative Frequencies of Infections*

Year	City of Aarhus			County of Aarhus			Both Areas combined		
	Records Reviewed	Infections		Records Reviewed	Infections		Records Reviewed	Infections	
		No	%		No	%		No	%
1956	1727	[illegible]09	1[illegible] 1	1497	233	15 6	3224	442	13 7
1957	17[illegible]2	[illegible]55	14 8	1437	2[illegible]1	15 5	3159	478	15 1
Total	3449	464	13 4	[illegible]934	456	15 6	6383	9[illegible]0	14 4

A survey of the series and the frequency of infections is given in Table I. It is seen that about 14 per cent of the *infants had clinical infections* within the first two months of life.

The types of infection are listed in Table II, which shows that purulent conjunctivitis occurred as the only manifestation in 5.5 per cent and in association with skin infections in *another 0.8 per* cent. Conjunctival irritation of short duration within the first few days of life, which might be referable to instillation of silver nitrate solution, was not recorded as conjunctivitis.

Table II. *Absolute and Relative Frequencies of the Individual Infections*

	No. of Cases	%	
Purulent conjunctivitis	352	5.5	
Typical pemphigus	254	4.0	512 = 8.0 %
Pemphigoid skin infection	205	3.2	
Typical pemphigus and purulent conjunctivitis	28	0.4	
Pemphigoid skin infect. and purulent conjunctivitis	25	0.4	
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Pneumonia and otitis media	6	0.1	
Total	920	14.4	

Napkin area dermatitis – whether pustular or not – was not included in the material.

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		No.	%		No	%		No	%
1956	17[illegible]7	[illegible]09	12 1	1497	[illegible]33	15 6	[illegible]4	44[illegible]	13 7
1957	17[illegible]	[illegible]55	14 8	1437	[illegible]	15 5	3159	4[illegible]	15 1
Total	3449	464	13 4	[illegible]934	456	15 6	6383	9[illegible]0	14 4

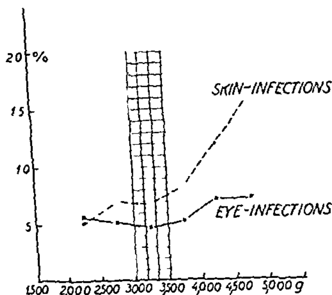


Fig 2 Percentages of eye and skin infections distributed according to birth weight

to the week of life in which the infections started The peak for eye infections occurred in the second week and that for skin infections in the third week After the fourth week of life the incidence was very low

The relation between eye and skin infections and the birth weight appears from Fig 2 It is seen that both types of infection were less frequent in infants with birth weights of 3 000–3 500 g or less while eye and particularly skin infections increased in frequency in infants weighing more than 3 500 g at birth

Table III shows that the relative frequencies of infections, especially of the skin were higher in boys than in girls

Table IV gives a survey of the frequency of infections in infants born at home and in the State Maternity Hospital for Jutland (Owing to the relatively small numbers infants born in Private Maternity Homes (122) and General Hospitals (95) are excluded from this survey) The two groups reveal a distinct difference in the percentages of eye infections The explanation

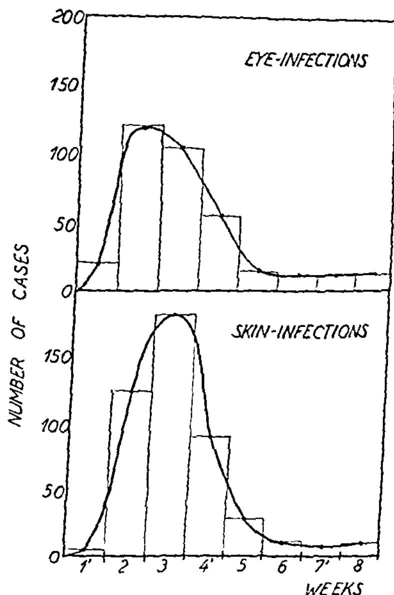


Fig 1 The frequencies of eye and skin infections related to the week of life in which the infections started

they were seen by the Health Visitor 43 per cent had been referred for medical treatment by the Health Visitor and 22 per cent were not given any treatment The infections were treated in hospital in 15 cases This figure represents 2 per cent of all infants with infections and 0 2 per cent of all the infants considered

Fig 1 shows the frequencies of eye and skin infections related

It must be assumed that the higher level of infections observed in the Maternity Hospital in 1957 was responsible for the increase in skin infections in infants discharged from this hospital, many of these infants must have been carriers of virulent staphylococci which did not give rise to manifest skin infections until after discharge

In infants born at home, the frequencies of both eye and skin infections occupied the same level in 1956 and 1957 and thus probably represent what might be called the endemic level of pyogenic infections during the first two months of life

SUMMARY

A review of 6 383 records compiled by the Health Visitors in the City and County of Aarhus (population 216 000) for 1956 and 1957 revealed an incidence of pyogenic infections of 14 4 per cent among infants up to the age of two months, *i e* pyogenic infection developed in every seventh infant within the first two months of life Purulent conjunctivitis occurred in 5 5 per cent and skin infections in 8 0 per cent.

The two types of infection reached their peaks in the second and third weeks of life

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Table III *Frequency of Infections in Boys and Girls*

	Records Reviewed	Eye Infections		Skin Infections		Total	
		No.	%	No.	%	No.	%
Boys	3 303	194	5 9	307	9 3	525	15 9
Girls	3,012	154	5 1	[illegible]04	6 8	386	13 1
Total	6 315	348	5 5	511	8 0	911	14 4

of the lower frequency of eye infections in infants born in the Maternity Hospital may be that in these cases the Health Visitor saw the infants for the first time at the end of the second week of life, at which time an acute eye infection may often have occurred and resolved (cf Fig 1)

Table IV *Eye and Skin Infections in 1956 and 1957 Distributed According to the Place of Birth of the Infants*

Place of Birth	1956					1957				
	Records Reviewed	Eye Infections		Skin Infections		Records Reviewed	Eye Infections		Skin Infections	
		No.	%	No.	%		No.	%	No.	%
At home	1835	113	7 1	130	7 [illegible]	1788	110	6 3	11[illegible]	6 4
Maternity Hospital	1120	5[illegible]	4 6	90	8 0	1115	54	4 8	1[illegible]6	11 3
Total	[illegible]955	165	5 6	220	7 5	[illegible]903	164	5 6	[illegible]38	8 [illegible]

In 1956, the incidence of skin infections differed only slightly in infants born at home and those born in the Maternity Hospital On the other hand, the frequency of skin infections increased in infants born in the Maternity Hospital in 1957

In 1957, infections among newborn infants in the Maternity Hospital were more frequent than usual The infections began to increase in the spring months and assumed the character of a minor epidemic in July This epidemic, which has been described by Stenderup *et al* (1959), seemed to be due to Staphylococcus aureus, phage type 80

of acidophilic cells, the percentage of superficial cells, and the percentage of karyopycnotic cells (Timonen and Purola, 1960) Œstrogen determination was very often impossible in trichomoniasis cases In some cases, however, a rough evaluation could be made

Cervical biopsy was carried out in 557 cases In all these cases abnormal cells had been found in the vaginal smear (Groups II to V) Not all cases belonging to Group II were histologically examined, however, whereas in all cases classed as Groups III to V biopsy specimens were obtained

To determine whether a correlation exists between parity and trichomoniasis relevant information was obtained from 400 consecutive menstruating trichomonas positive patients and 400 consecutive trichomonas negative patients

Results

Trichomonas vaginalis was found in 1,900 smears (19 9 per cent) out of 9 550 taken at the hospital However, of the 5,000 samples from private patients only 600 were positive (12 per cent) The latter series is very heterogeneous however as it includes specimens sent from provincial hospitals Five hundred and five cases from one Helsinki gynæcologist were also examined Among these cases 44 were trichomonas positive (8 7 per cent) The widely different frequencies (0–70 per cent) of trichomonas infestation reported in the literature are explained by varying socio-hygienic conditions among different peoples and social groups (Buxton Weinman, Johnsson Forst Wroblewski and Conte 1958 cf Trussell and Plass 1940) This is also apparent from the variation in this series between private and public hospital patients

There are also great differences with regard to age which is only natural as the hormonal secretion and also the frequency of sexual intercourse which may be responsible for the transfer of trichomonas vary with age Fig 1 shows the age distribution Infection is commonest during the later years of sexual maturity with a slight peak around the age of 40 The curve also illustrates the well known fact (Künstler 1884) that trichomoniasis rarely

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TRICHOMONIASIS

Ætiological and Histo-pathological Aspects

BY

S TIMONEN AND E. VARTIAINEN

The purpose of the *present study* is to investigate the relation of vaginal trichomoniasis to œstrogen activity and to atypical epithelial changes found in the portio vaginalis uteri

Material and Methods

The series consists of 9,550 vaginal smears taken in the Out patient Department and Wards of Helsinki University Central Hospital, Departments of Obstetrics and Gynæcology I and II The incidence of trichomoniasis was further determined in a series of 5,000 private patients and another 505 patients the latter all being the patients of one gynæcologist

The samples were stained according to Papanicolaou's original method (Papanicolaou and Trout 1943) The same person (Timonen) examined all samples To check the reliability of the method trichomonas cultures were made in 100 cases, the following results being obtained 100 positive smears and 98 positive cultures (Vartiainen and Ryynänen 1959)

In the examination of the smears the usual malignancy classification was carried out (Grades I to V) Classification of the vaginal flora was made in four grades according to af Heurlin (1914) The degree of œstrogen activity was evaluated by the percentage

of acidophilic cells, the percentage of superficial cells, and the percentage of karyopycnotic cells (Timonen and Purola, 1960) Œstrogen determination was very often impossible in trichomoniasis cases In some cases, however, a rough evaluation could be made

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Table I The Frequency of Trichomonas Vaginalis (TV) in Certain Gynæcological Diseases

	No. of Cases	TV positive	Per cent
Whole series	9 550	1 900	19 9
Cervicitis	1 434	502	35 0
Pre-menstrual tension and other symptoms clinically explained as hyper-œstrogenism	276	76	28 4
Myomata uteri	491	129	26 5
Endometriosis	173	44	25·4
Metropathia hæmorrhagica	140	34	24·3

II The low incidence of trichomoniasis in uncomplicated pregnancy is striking In many previous investigations the results have been the opposite (cf Trussell, 1947, Bernstine and Rakoff, 1953) Our observation is not an isolated one, however as we have earlier (Timonen and Goltner 1959) found 13 5 per cent trichomoniasis in 414 pregnancy samples from the same clinic Comparison should be made with a series from healthy subjects but such data were not available Statistics are needed based on samples taken from married women of the same age groups and from the same environment. The only data of any value for comparison are the results obtained in a cancer detection investigation carried out in 1956 the series consisting of the female staff of the Post and Telegraph Office of Helsinki (Parviainen 1957) In about 500 healthy female civil servants the percentage was 15 The incidence of trichomoniasis was not higher during pregnancy in our present series either The influence of

Table II The Frequency of Trichomonas Vaginalis (TV) in 698 Normal and Complicated Pregnancies

	No. of Patients	TV-positive	Per cent
Normal pregnancy	385	53	13 8
Abortus imminens, incipiens	216	40	18 6
Residua post abortum	97	35	36 0



Fig 1 The percentage of trichomonas vaginalis vaginitis in different age groups The total number of cases is 1,900

occurs in old age An interesting secondary observation, however, was the fact that there was another slight rise in patients over 70 years old

When investigating the occurrence of trichomoniasis in connection with various gynæcological diseases, particular attention was paid to hormonal disorders The incidence of trichomoniasis in connection with cervicitis was also investigated (Table 1) In studying the results it should be remembered that each disease has a characteristic age incidence Thus, in the same hospital, the average age of the myoma patients is 44 4 years (Timonen and Purola, 1960) and of the endometriosis patients 36 8 years (Timonen and Krokfors, 1959) The trichomoniasis frequencies for these ages taken from curve I, are 24 per cent and 25 per cent respectively The commonest age group for hyper œstrogenism (urine assay and cytological estimation) was 36 to 40 years and for this age group the percentage incidence of trichomoniasis is 25 There is thus no significant increase in the incidence of thrichomoniasis It should be noticed, however, that while high œstrogen secretion does not seem to protect (cf Chappaz, 1946) patients against trichomoniasis it may be a pre-disposing factor The frequency of trichomoniasis in cases of clinical vaginitis was not investigated A high percentage would presumably be found here, as in cervicitis

A total of 698 samples were taken from patients during normal and complicated pregnancies Their distribution is shown in Table

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Residua post abortum	97	35	36·0

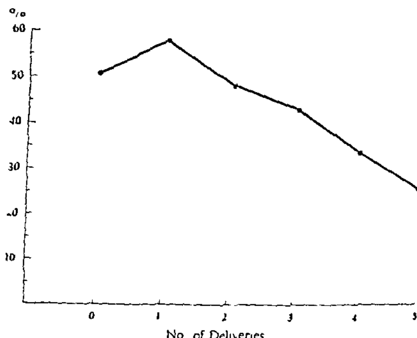


Fig 2 The relative frequency of trichomonas vaginalis vaginitis in different parity groups The total number of patients is 800 of whom 400 are trichomonas positive and 400 trichomonas negative

pregnancy on the degree of severity of the disease is a different problem, which was not considered in these investigations

Previously we analysed (Timonen and Goltner, 1959) those cases of imminent abortion in which the treatment was successful and the pregnancy was preserved and those in which treatment failed and abortion occurred In the former group, the trichomoniasis percentage was 17 2 and in the latter 32 3 This tallies well with the results of the present investigation, *viz* that in post abortal conditions trichomoniasis occurred in 36 per cent of cases It would, however, be unjustifiable to draw any conclusions on the basis of this observation as to the possible role of trichomoniasis in the ætiology of abortion So far as is known trichomonas does not occur in the cervical canal (Donné 1936) Infection caused by bacteria occurring in connection with trichomonas may possibly influence the prognosis of imminent abortion

The relative occurrence of trichomoniasis in the various parity groups can be seen from Fig 2 Krokfors (1960) has recently

arried out an investigation on the relationship between gynæ-
ological diseases and parity The curve in Fig 2 diverges markedly from the rising linear relationship shown to parity in cervical carcinoma and also from the rising parabola in hyper œstrogenism (Timonen and Krokfors, 1959)

Estimations of hormonal status based on examination of vaginal smears in patients with trichomoniasis are very uncertain (Pundel, 1952) In some cases in which there were fewer trichomonads (possibly due to a more recent infection or a less virulent one) we carried out œstrogen determinations The value of determinations of this kind is limited and they should be assessed accordingly The following results were obtained in 760 cases œstrogen effect low in 29 per cent normal in 47 per cent high in 24 per cent In the general cases from the same hospital the rate of incidence of hyper œstrogenism by cytological assessment in gynæcological patients was 13 9 per cent (Timonen and Krokfors 1959) This series includes older age groups however in which there are fewer trichomonas positive patients For comparison we used the frequency of hyper œstrogenism in the age group 36–40 in which the incidence reached a peak The control value is thus 18 According to this hyper œstrogenism seems to be slightly commoner (24 per cent) in trichomoniasis patients than in the controls

The vaginal flora was classified in 1 860 trichomoniasis cases, 109 cases (6 4 per cent) were classified as Grades I and II *viz* a more or less normal vagina 546 cases (29 3 per cent) as Grade III and 1 206 patients (64 3 per cent) as Grade IV For comparison, it should be mentioned that Labhardt (1955) obtained the percentages 8 2 24 5 and 67 3 for the corresponding grades Vartiainen and Ryynänen (1959) classified the vaginal flora in a series of cases of trichomoniasis from our hospital They classed 18 8 per cent as Grades I-II and 81 2 per cent as Grades III-IV

It is well known that trichomonas has a cytotoxic effect and that various abnormal types of cells therefore occur in association with infection (Pundel 1952) These may render cytological cancer diagnosis difficult No connection between the nuclear and tissue changes caused by trichomoniasis and the actual premalig

Table III *Frequency of Different Cytological Groups according to Papanicolaou in 1,900 T positive Smears and 7,650 T-negative Smears As a Control a Similar Grouping of a Series of 10,000 Consecutive Cases Published Earlier from the Same Laboratory (Timonen, 1958) is Shown*

	Trichomonas-positive Per cent	Trichomonas-negative Per cent	Timonen, 1958 Per cent
Group I	62 6	82 26	80 9
II	33 2	13 4	14 3
III	2 3	2 5	2 7
IV	1 5	1 1	1 2
V	0 4	0 7	0 9

nant and malignant cell changes has, however, been conclusively demonstrated (cf Dyroff, 1957) The distribution of trichomonas-positive samples according to the cytological malignancy scale is seen from Table III For comparison the distribution of 10,000 consecutive samples from a previously published series (Timonen, 1958) is given in this Table The percentage distribution in the frankly malignant groups is more or less the same in both series On the other hand, inflammatory atypias, primarily of Group 2, are considerably more abundant in the trichomoniasis series

If the *erroneous positive smear* reports in the two series are considered, there is a considerable difference In the earlier series the number of erroneous positive reports was 44/10,000 (0 44 per cent) while in the present trichomonas positive series it was 14/1 900 (0 74 per cent) In the trichomonas negative series the number of erroneous positive reports was 36/7 650 (0 47 per cent) Thus we find that trichomonas caused an increase in the erroneous positive reports The difference does not seem large if we bear in mind the very considerable difference between the numbers of erroneous positive reports in different series (Limburg, 1956), but the series under discussion are from the same laboratory and interpreted by the same person and the difference therefore is significant In the earlier published series (Timonen, 1958) no increase was observed in the number of erroneous diagnoses due to trichomonas infection In the light of the results now obtained it seems probable, however, that insufficient atten-

Table IV *Results of the Histological Examination of 557 Cervical Biopsy Specimens Taken from 140 Trichomonas positive and 417 Trichomonas nega ve Cases All Showed Abnormal Cell Characteristics (Groups II–V) in the Vaginal Smear*

Histological Diagnosis	Trichomonas-positive		Trichomonas-negative	
	No. of Cases	Percentage	No. of Cases	Percentage
Cervicitis	58	41 4	165	37 1
Cervical polypus	12	8.6	25	6 0
Pseudo-erosio (ectopia)	20	14 3	84	20 2
Pseudo-erosio papillaris	6	4 3	27	6 5
Erosio vera	39	27.8	124	29 7
Cervical hyperplasia	1	0 7	10	2 4
Benign tumours	2	1 4	1	0 2
Keratinization	20	14 3	47	11 3
Epidermidization	21	15 0	57	13 7
Stratified epithelium altered by inflammation	11	7 9	25	6 0
Basal hyperactivity	12	8 6	21	5 1
Hyperactive epithelium	9	6 4	28	6 7
Suspect for carcinoma *in situ*	8	5-7	23	5 5
Carcinoma *in situ*	6	4 3	20	4 7
Infiltrative carcinoma	7	5 0	37	8 9
Total	140		417	

tion was paid to trichomoniasis earlier and that its diagnosis was uncertain

The results of histological examination of 557 cases are given in Table IV Biopsy was carried out in all cases in which cells belonging to Groups 3–5 were observed Many of the cases of Group 2 were also examined histologically There was a considerable rise in the inflammatory atypias in the trichomonas positive group This was particularly evident in the groups 'keratinization stratified epithelium altered by an inflammation and 'basal hyperactivity There was also a higher percentage in connection with cervical polypus On the other hand there was no increase in the frankly malignant changes in the trichomoniasis group Suspected carcinoma *in situ* and carcinoma *in situ* together probably represent clear pre cancerous stages These are equally frequent in both groups The group hyperactive epithelium may possibly

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œstrogenic diseases This however was not the case, on the contrary, in these diseases either normal or slightly increased rates of incidence were observed This finding constitutes evidence against the importance of hypo-œstrogenism

A hyper œstrogenic condition has also been suggested as a factor promoting trichomoniasis (Herold and Losche 1953, Vartiainen and Ryynänen, 1959) Here abundant formation of glycogen as a result of the influence of œstrogens was considered to be a factor promoting infection When treatment was based on this good results were obtained in the treatment of trichomoniasis with progesterone (Zilliacus and Vartiainen, 1960) If there is a correlation between hyper œstrogenism and trichomoniasis then there ought to be an increased trichomonas incidence in hyper œstrogenic diseases This was not the case, however and only slightly increased values were occasionally observed On the other hand, the correlation between trichomoniasis and parity was of an entirely different type from that of hyper œstrogenism Thus, if there is any correlation between trichomoniasis and hyper œstrogenism, it is slight and indirect This does not exclude the possibility that hypo or hyper œstrogenism have some indirect effect upon the clinical picture of trichomoniasis It is not impossible that both hypo- and hyper œstrogenism have an unfavourable effect upon the prognosis of this disease but this is in the realm of speculation

When we consider the obvious cytotoxity of trichomonads, an association with carcinogenesis does not in itself appear too far-fetched The results obtained in the present investigation however do not support this The number of malignant or premalignant histological findings in the trichomonas group was not increased On the other hand, inflammatory changes in the epithelium were commoner

Of these keratinization is the most interesting Its occurrence has been connected with carcinogenesis because the cells of epidermoid carcinoma have a tendency to form keratin However, some other process must be implicated Keratinization in itself is a very common phenomenon in the vagina it is regularly observed with prolapse and thus is the result of mechanical irritation Yet no raised incidence of carcinoma in association with prolapse has

contain some pre-cancerous cases but to distinguish between these and inflammatory cases by means of histological methods is not possible It seems, however, that this type of epithelium is not the result of the influence of trichomonas, a circumstance that argues strongly against any carcinogenetic property of trichomonas The obvious increase of keratinization due to the influence of trichomonas is interesting (Dyroff, 1957)

Discussion

In culture, œstrogens have no direct effect upon the growth of trichomonads (Kupferberg and Johnsson, 1941) Indirectly, however, by way of the vaginal glycogen metabolism and pH regulation, the œstrogens play an important role in the creation of a favourable milieu for infection The age curve of trichomoniasis falls rather abruptly around the age of 55 It remains low during old age with the exception of a slight rise in the 70 year group This rise is particularly interesting as it was also evident in the age curve of the series of cases of relative hyper-œstrogenism (Timonen and Krokfors, 1959), as well as in the age curves of ovarian tumours and carcinoma of the corpus uteri (Krokfors, 1960) We may conclude that some kind of œstrogen effect upon the vaginal mucosa is necessary for the thriving of trichomonas and that this is absent from the normal senile vagina

In the light of this age curve, theories suggesting that trichomiasis is connected with hypo-œstrogenism (cf Chappaz, 1957) do not seem plausible It must be remembered, however, that for the growth of trichomonads the optimal pH (pH 5 5–5 8) is somewhat higher than the optimal pH reported for B Doderlein (pH 3 5–4 5) Looking at it from this point of view, it might possibly be assumed that a rise in the pH because of a lack of œstrogens would increase the chances for trichomonas to thrive A rather high frequency of hypo-œstrogenism was actually observed in vaginal smears but the reliability of this method in connection with trichomoniasis is so doubtful that no great importance can be attached to the results If a significant correlation existed between hypo œstrogenism and trichomoniasis then there should be a reduced trichomoniasis incidence in hyper

œstrogenic diseases This, however was not the case, on the contrary, in these diseases either normal or slightly increased rates of incidence were observed This finding constitutes evidence against the importance of hypo-œstrogenism

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been observed The keratinization occurring with trichomoniasis is probably the result of an adaptive reaction of the vaginal mucosa Possibly the chemical irritation caused by the protozoa first leads to increased cornification Hence, initially there is a condition that simulates an œstrogen effect, but as the infection continues the nuclei become gradually resorbed and the cytoplasm keratinized Thus, here keratinization is the end result of the 'defense stage' leading to healing of the mucosal injuries caused by trichomonas At the final stage histological examination reveals stratified epithelium, the superficial cell layers of which are keratinized and from which the glycogen containing cells of the middle layer are missing This keratinization is in no way connected with carcinogenesis

Neither does the correlation with parity suggest any causal relation to carcinoma of the cervix In cytological diagnosis trichomonas does cause erroneous positive diagnoses, a fact which must be attributed to the cyto- and nucleotoxic effect of this organism

SUMMARY

1,900 cases of trichomoniasis are reported, which were collected from 9,550 vaginal smears from the Departments of Obstetrics and Gynæcology I and II, Helsinki University Central Hospital The trichomonas incidence was 19 9 per cent A series of 5,000 private patients is also presented, in which the trichomonas incidence was 12 per cent In a separate series of 505 patients of one gynæcologist the incidence was 8 7 per cent

Trichomoniasis is commonest between the ages of 30 and 50 after which there is a considerable drop and a slight rise in the age group over 70

The trichomonas incidence in some gynæcological diseases is reported Slightly increased values were obtained in association with clinical hyper-œstrogenism and myoma In endometriosis and metropathia hæmorrhagica the incidence was not increased

The relation between parity and trichomonas was investigated in 800 cases Trichomonas was commonest in bipara and thereafter a descending curve was obtained

No clear correlation between hyper- or hypo œstrogenism and trichomonas vaginitis could be observed This does not, however, exclude the possibility of an indirect influence upon the character of the trichomonas infection

Histological and cytological examinations did not indicate that trichomonas vaginitis increases the incidence of malignant changes, but on the other hand, the number of erroneous positive cytological diagnoses increased The commonest of the histological changes caused by trichomonas were keratinization, basal hyperactivity and slight inflammatory changes in the stratified epithelium

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From the Helsinki University Central Hospital, Departments of Obstetrics and Gynæcology I and II (Professor Aarno Turunen and Professor Paavo Vara)

ON THE ÆTIOLOGY OF ENDOMETRIOSIS

BY

AARNO TURUNEN SAKARI TIMONEN AND BERNDT JOHAN PROCOPÉ

In discussions on the pathogenesis of endometriosis principal emphasis has been on the origin of the endometrial tissue The oldest theory is that advanced by Ivanoff-Meyer (1898), according to which the origin is from the serosa through differentiation This theory, in a modified form, still finds support It has proved necessary, however, to extend the theory of a sero-epithelial origin to include all the mesenchymal tissue in and around the area of the genital canals As Heim (1959) sees it, a sero epithelial genesis resulting from irritation by menstrual blood should also be taken into consideration (Levander and Normann, 1955) It was in this form (Bruckentheorie) that Heim last presented his theory The occurrence of endometriosis by spread along vascular routes has been considered probable in exceptional cases (Philipp and Huber, 1939, Limburg, 1949) Migration of endometrium along the lymphatics to the lymph nodes has also been considered possible (Javert, 1952)

However, during recent decades the predominating theory has been Sampson s (1921) implantation theory, according to which the condition arises from endometrial cells which through retrograde menstruation have found their way into the abdominal cavity This explanation is attractive in its simplicity and would definitely explain the majority of observed cases of endometriosis

According to another version of this theory, the tissue fragments causing implantation, may also originate from a tubal endometriosis focus (Philipp and Huber, 1939, Turtola, 1942) Discordant views are held on the proliferative capacity of the endometrial particles Experiments carried out during recent years indicate, however, that proliferation is possible (Scott, and Wharton, 1957, Ridley and Edwards 1958)

Independently of which of the above theories the location of the endometriosis accords with, it is further recognized that hormonal and constitutional factors also play a part in the disease The dependence of endometrial growth on œstrogens and the fact that endometriosis only occurs in sexually mature individuals are clear indications of endocrine involvement Experimental results also point in this direction It should be mentioned, for instance, that Scott and Wharton (1957) obtained the best results in implantation experiments on a Rhesus monkey by administering œstrogens and progesterone in turn On the other hand, the occurrence of the disorder in patients with hypoplastic genitalia or in connection with developmental anomalies suggests the presence of a constitutional disposition (cf Albrecht, 1955, Turunen 1939 1954) A high rate of occurrence in connection with myomatosis also hints at a combined hormonal and constitutional background

Since comparatively few investigations on endometriosis have taken into account the interaction of these two factors we have in the present study concentrated particularly upon an investigation of the constitutional and endocrine factors as represented in a clinical series

Present Series and Method

The series consists of 381 patients with endometriosis operated on at the Women s Clinic of the Helsinki University Central Hospital during the period 1955 to 1958, the diagnosis of endometriosis having been histologically confirmed in every case Cases in which there was only adenomyosis interna were not included in the investigation Clinical and histological records of all

patients were available In the clinical examination attention was paid to the location of the endometriosis, and to the patient's height, weight, and blood pressure In 101 cases endometrial biopsy specimens or samples obtained at operation from the area of the endometrium were available

Vaginal smears for the estimation of the œstrogen effect were obtained in 103 cases The specimens were stained according to Papanicolaou's original method (Papanicolaou and Traut, 1943) The degree of the œstrogen effect on the vaginal cells was determined according to Timonen and Purola (1960) In addition, hormone determinations were made in 26 cases from 24-hour urine Hormone determinations were carried out as follows F S H (Bradbury, Brown, and Brown, 1949), œstrogen determination by a biological method (Ahlmark *et al*, 1954), pregnandiol determination (Jensen, 1955), and 17 ketosteroid-determination (the C method, Jensen and Totterman, 1952)

Results

Since it has already been established (cf Timonen and Purola, 1960, Timonen and Vaananen, 1959) that increased œstrogen secretion plays a decisive role in the genesis of uterine myoma, those endometriosis cases in which myomata occurred were grouped separately Among 381 cases of endometriosis myomata were present in 158 cases (41 5 per cent) There were thus 223 cases of pure endometriosis The average age of all patients was 36 8 years being 34 2 years in the group of pure endometriosis, and 39 9 per cent in the myoma with endometriosis group (Fig 1) The difference between the peaks in the curves for pure endometriosis and for myoma with endometriosis is ten years This agrees with the well known clinical fact that endometriosis occurs in younger patients than myoma In Krokfors (1960) series, for instance the average age of the endometriosis patients was 38, while the average age of myoma patients varied between 40 and 45

It will be seen from Table I that the endometriosis patients were slightly taller than the controls their weights however

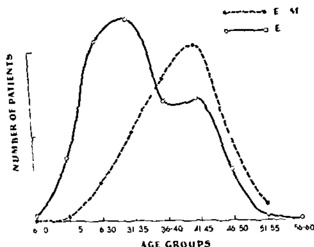


Fig 1 Age distribution of 223 patients with endometriosis alone and 158 patients with endometriosis and uterine myoma

Table I *Mean Age Height Weight and Blood Pressure of 381 Cases of Endometriosis As a Control the Mean Values of a Group of 1 000 Patients of Corresponding Age without Myoma are Shown* (Timonen and Purola 1960)

	Age	Height	Weight	Systolic Blood Pressure	Diastolic Blood Pressure
Whole series	36 8	160 1	62 9	137 0	85 7
Control	same	159 4	61 5	125 0	79 5
Endometriosis alone	34 2	160 1	62 4	133 7	84 6
Control	same	159 4	61 0	124 0	79 0
Endometriosis and myoma	39 9	160 0	63 6	138 8	88 3
Control	same	159 4	63 0	130 0	82 0
Myoma alone (Timonen and Purola)	44 4	159 1	68 8	147 7	93 6
Control	same	159 4	64 3	136 0	84 0

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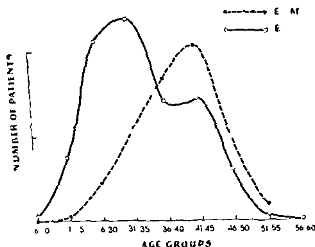


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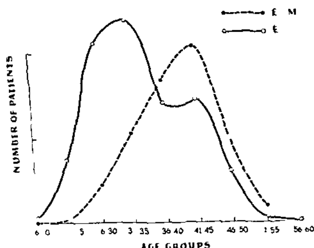


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being the same As compared with the controls, the endometriosis patients did not show the increase in weight of about 4 kg which was typical of myoma patients On the other hand, their blood pressure, systolic and diastolic, was higher than the controls, even though the difference was not so marked as in the myoma series (Timonen and Purola, 1960)

The location of the endometriosis, will be seen in Table II Ovarian endometriosis predominated, a fact observed in previous studies

Table II *The Main Localization of Endometriosis in 381 Cases Examined Histologically*

Ovarial endometriosis	243
Serosal manifestations of endometriosis on the bladder, uterus, sacro-uterine ligaments, and rectum	132
Endometriosis of the omentum	1
Vaginal and cervical endometriosis	5

Particular attention was paid to the histological findings which threw light on the hormonal status of the patients (Table III) Endometrial specimens were obtained in 101 cases, progestational changes in the endometrium were observed in 39 cases, and endometrial hyperplasia was found in 40 cases A normal proliferative stage corresponding to the cycle occurred in 11 cases only Endometrial polypi were observed in 13 cases An atrophic endometrium, however, was found in only 5 cases The high proportion of hyperplasia in our series is striking particularly in view of the fact that in the literature low percentages have been reported (Scott and TeLinde, 1950 for instance found endometrial hyperplasia in only 2 per cent of cases) It is of particular interest to ascertain whether hyperplasia or, on the other hand, progestational changes in the endometrium were particularly frequent in connection with pure endometriosis or in cases of endometriosis with myoma Progestational changes were observed in 11 cases of pure endometriosis and in 26 of myoma with endometriosis Hyperplasia, on the other hand occurred in connection with myoma in 33 cases and with pure endometriosis

in 7 cases, thus being more frequent in the myoma group In 9 cases of pure endometriosis and in only one case in the myoma with endometriosis group, histological evidence was obtained of an active corpus luteum Although the figures are very small, they suggest that endometrial hyperplasia is more frequent in conjunction with myoma, while in endometriosis the endometrium is often secretory

Table III *Results of Histological Examination of 381 Patients Operated on for Endometriosis*

		No. of Cases	Per cent
Endometrium			
Progestational state		39	39
Proliferative tate		11	11
Hyperplasia	7		
Cystic glandular hyperplasia	33		
Hyperplasia		40	40
Polypus		13	13
Atrophic endometrium		5	5
Carcinoma		3	3
Decidual reaction		2	2
Endometritis		4	4
Myometrium			
Myomata		158	41 5
Adenomyosis		21	5 5
Ovaries			
Polycystic ovaries		27	7 2
Cysta simplex		11	2 9
Corpus luteum	10		
Cystic corpus luteum	12		
Corpus luteum		22	5 8
Cystadenoma serosum papilliferum		1	
Cystadenoma pseudomucinosum		3	
Brenner tumour		1	
Fallopian Tubes			
Chronic salpingitis		1	
Tubal abortion		1	

It has previously been shown (Timonen and Vaänänen, 1959) that endometrial hyperplasia is comparatively rare in young patients with myoma but that its incidence increases with age The age factor is probably also of significance in the present series with its rather high frequency of myoma, 41 8 per cent, the higher average age of these patients possibly influencing the frequency of hyperplasia

The histological specimens from the ovaries were less revealing Polycystic ovaries occurred in 27 cases (7 2 per cent) a circumstance which might be related to the occurrence of hyperplasia in the endometrium

Vaginal smears were taken in 103 cases (Fig 2) In 50 cases specimens from the eighteenth cyclic day or later were available In 30 (60 per cent) of the latter the œstrogen effect was estimated to be stronger than normal This estimation was made on the basis of percentages of acidophilic and superficial cells If the percentage exceeded 50, the case was referred to the group hyper-œstrogenic

The significance of the progesterone effect as determined from vaginal smears is not always reliable In 22 of the above mentioned 30 specimens classified as hyper-œstrogenic, a progesterone effect was absent Of these specimens 21 belonged to the pure endometriosis group and 9 to the myoma with endometriosis group Hyper-œstrogenism as determined by vaginal smears is thus equally frequent in the group of pure endometriosis and in that of endometriosis with myoma As already mentioned, however, endometrial hyperplasia occurs more frequently in connection with myoma than with endometriosis

The œstrogen effect was rated as weak in 7 cases This corresponds approximately with the endometrial histology in which atrophy was observed in 5 specimens out of 101

Fig 2 shows the cytological œstrogen determinations distributed according to the day of the menstrual cycle Although there is a comparatively small number of specimens for some days and the mean value cannot therefore be considered entirely reliable, the conclusion to be drawn from the average curve seems to be that in endometriosis ovulation takes place comparatively often since the curve falls, although slightly, from the middle of the cycle on

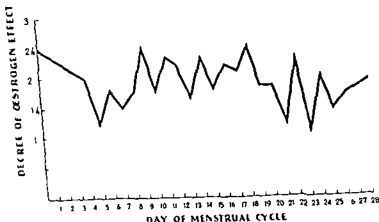


Fig 2 The average values of œstrogen effect (Œ) distributed according to the day of the menstrual cycle (103 endometriosis cases)

wards The rise of the curve in the last few days of the cycle, a rise that also occurs in the first days of the cycle, is not statistically significant

When these figures are examined, it will be observed that they confirm our earlier statement (Timonen and Krokfors 1959) that according to the vaginal smear picture hyper œstrogenism occurs with approximately equal frequency in endometriosis as in connection with myoma If the œstrogen status is evaluated on the evidence of the histological picture of the endometrium alone the findings suggest that hyper œstrogenism is more frequent in the myoma with endometriosis group than in the pure endometriosis group Thus the endometrium of patients with pure endometriosis appears to be less sensitive to œstrogens than the cells of the vaginal mucosa An alternative interpretation of the phenomenon would be that in the latter group the endometrium receives less œstrogens than the vagina (receptor deficiency)

Regardless of the stage of the cycle hormone determinations were performed on urine one day prior to operation in 26 cases (Table IV) In this group of patients the average age was 38 years and average day of the menstrual cycle at operation the

Table IV *Hormone Assays on 26 Endometriosis Patients*

No	Age	Day of Cycle	Hormone Assays								Histological Examination				
			FSH	Œstr	Pregn	17-KS	AC	SC	PC	Œ (Smear)	Pe	Endometrial hyperplasia	Secr	Myoma	Acl
1	34	15	60	165		6 2	60	85		*3*	—		—	+	
2	47		40	250		3 1									
3	38		40	*1 320*		7 8								+	
4	26	19	10—40	330		13 3	10	40		1					
5	27		10—40	660	0 7										
6	40		40	330										-	
7	42	20	10—40	330	1 3	8 1	40	60		2	—			+	
8	46	16	10—40	*1 000*	1 8	7 7	50	80		*2 5*	—	+			
9	50		40	165	1 1	4 6						+		+	
10	44	21	10	165	0 9	9 9	10	50		1	+	+		—	
11	38		40	580	0 7	3 9						+			
12	46	22	10	165		7 1	70	80	80	- 5	—	+		-	
13	37		40	330	1 1										
14	26	16	40	330		4 7	50	60		-	—			+	
15	48	22	40	*1 000*		5 6	50	90		2 5	—			—	
16	38		10—40	*1 570*		12 1									
17	42	19	10—40	250	0 8	5 6									
			80—160	*1 000*											
18	2[illegible]	12	10—40	330	0 7	6 9	70	40		2					
		24	40	250	0 9	4 8									+
19	33	14	40	*1 650*	3 2	8 3									
20	23	16	40	330	0 2		40	20	60	1 5	—				
21	31	7	10—40	*1 650*	0 6	7 9									
22	48	19	40	330	3 8	5 3							+	+	+
23	34	9	10—40	660	1 3	7 2	80	90	70	*3*					
		18					90	80	80	*3*	—				
24	43	23	40	165		4 7	20	30		1	+		+		+
25	37	14					70	50	70	- 5					
		17	10—40	330		5 7									
		19											+		
26	45	12	10	660		5 2	70	60	60	2 5			-		
Mean	38	17		560		6 8	53	60		2					

FSH = FSH determined from 24 hr urine in M U
Œstr = œstrogenic hormones in 24 hr urine in I U
Pregn = pregnandiol in 24 hr urine in mg
17 KS = 17 ketosteroids in 24 hr urine in mg
Ac = Percentage of acidophilic cells
Sc = Percentage of superficial cells
Pc = Percentage of cells with pycnotic nuclei
Œ = Degree of œstrogen effect on vaginal cells
Pe = Progesterone effect on vaginal cells
Secr = Progestational changes in the endometrium
Acl = Active corpus luteum

seventeenth The average urinary œstrogen output was 560 I U/24 hrs and the 17 ketosteroid secretion 6 8 mg/24 hrs Cytological hyper œstrogenism was observed in 6 out of 15 cases, histological hyperplasia of the endometrium in 5 out of 9 cases and on the basis of the urine values, hyper œstrogenism (1,000 I U) in 8 out of 26 cases

The progestational status was estimated on the basis of changes observed in the endometrium, on the appearance of a corpus luteum, pregnandiol secretion, and changes in the vaginal cells Signs of an active corpus luteum were observed in 6 out of the 10 cases which were operated on on the eighteenth cyclic day or later

In the vaginal cell picture the percentage of acidophilic cells was 53 and the percentage of superficial cells 60, which gives an œstrogen value of 2 For the seventeenth day of the cycle these values can be considered to be within normal limits Likewise an average urinary output of œstrogens (560 I U) is within normal limits Both, however lie at the upper limit of the normal range

In some cases determinations of œstrogens carried out according to different methods gave results which appeared contradictory Thus, in the vaginal smear in Case 1 a strong reaction was observed whereas the œstrogen secretion into the urine was low In Case 12 vaginal cytology and the endometrium suggested high values while the urinary secretion was low The apparent contradiction depends on the fact that the endometrium and the vaginals cells both give information on the patient s œstrogen balance retrospectively while the urine shows the situation obtaining on the day of examination Also, about 5 to 10 days are necessary to elicit a strong vaginal cell reaction while the growth of hyperplastic endometrium requires 3 to 4 weeks and thus the time factor is different for all the three methods available for the determination of œstrogen effect

The simultaneous use of all three methods is of advantage because in this way it is possible to obtain information on the patient s œstrogen balance from the day of examination and for several weeks beforehand. Sometimes, if one of the three tests shows a value higher than normal the patient is, or was for the last few weeks before the operation subject to a strong œstrogen

Table IV *Hormone Assays on 26 Endometriosis Patients*

No	Age	Day of Cycle	Hormone Assays								Histological Examination				
			FSH	Œstr	Pregn	17-KS	AC	SC	PC	Œ (Smear)	Pe	Endometrial hyperplasia	Secr	Myoma	Acl
1	34	15	60	165		6 2	60	85		3	—		—	+	
2	47		40	250		3 1									
3	38		40	1 320		7 8								+	
4	26	19	10—40	330		11 3	10	40		1					
5	27		10—40	660	0 7										
6	40		40	330										−	
7	42	20	10—40	330	1 3	8 1	40	60		2	—			−	
8	46	16	10—40	1 000	1 8	7 7	50	80		2 5	—	+			
9	50		40	165	1 1	4 6						+		−	
10	44	21	10	165	0 9	9 9	10	50		1	+	+		—	
11	38		40	580	0 7	3 9						+			
12	46	22	10	165		7 1	70	80	80	2 5	—	+		−	
13	37		40	330	1 1										
14	26	16	40	330		4 7	50	60		2	—			−	
15	48	22	40	1 000		5 6	50	90		2 5	—			—	
16	38		10—40	1 570		12 1									
17	42	19	10—40 80—160	250 1 000	0 8	5 6									
18	22	12	10—40	330	0 7	6 9	70	40		2					
		24	40	250	0 9	4 8									+
19	33	14	40	1 650	3 2	8 3									
20	23	16	40	330	0 2		40	-0	60	1 5	—				
21	31	7	10—40	1 650	0 6	7 9									−
22	48	19	40	330	3 8	5 3							+	+	
23	34	9	10—40	660	1 3	7 2	80	90	70	3					
		18					90	80	80	3	—				−
24	43	23	40	165		4 7	20	30		1	+		+		
25	37	14					70	50	70	- 5					
		17	10—40	330		5 7							+		
		19											+		
-6	45	12	10	660		5 2	70	60	60	2 5					
Mean	38	17		560		6 8	53	60		-					

FSH = *FSH determined from 24 hr* urine in M U
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Œ = Degree of œstrogen effect on vaginal cells
Pe = Progesterone effect on vaginal cells
Secr = Progestational changes in the endometrium
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œstrogenism in 30 per cent of the whole series of cases F S H determinations in the urine suggested that the hyper œstrogenism was of hypophyseal origin In the young endometriosis patients ovulation seemed to be fairly frequent

Discussion

It is obvious that œstrogens are necessary for the occurrence of endometriosis, as the condition occurs only after puberty and there is a regression of symptoms in castrated individuals To what extent hyper œstrogenism is responsible for the occurrence of the disease is, however, quite a different matter It is seen from Fig 1 that so called pure endometriosis may occur even at a relatively early age, while endometriosis accompanied by myoma is concentrated at the usual age of occurrence of myoma, *i e* about ten years later We have previously shown that on an average hyper œstrogenism occurs about six to eight years earlier than myoma (Timonen and Purola, 1960) Here the increased secretion of œstrogens constitutes a natural part of the mechanism of development of myoma

In the ætiology of pure endometriosis however because of the earlier age of occurrence, there must be some other factor with a very strong effect which may provoke the disease at any age after the menarche If this factor is strong enough, the part played by the œstrogens in the ætiology of the disease may be insignificant Thus Weyeneth (1933) examined 40 children aged 14 or under and found that four of them had endometriosis, always in conjunction with some developmental disturbance The œstrogen values were not excessive Similar cases in which endometriosis was clearly present without high œstrogen values have been published by others (Zondek Unger, and Leszynski 1953)

Thus if the non œstrogenic factor is strong enough, it is able by itself to produce the disease In the cases mentioned above this is what happened (congenital cervical obstruction or vaginal aplasia for instance)

In a milder form the structural deficiency occurs in endometriosis patients as hypoplasia of the reproductive organs In 16 per

effect It will thus be seen from the results given in Table IV that there are signs of hyper-œstrogenism in 14 out of 26 cases, i e in half the cases

If the whole series is combined in the same way, in 71 cases one of the tests indicated hyper œstrogenism. Considering the cases in which at least one of the tests was carried out, there was hyper-œstrogenism in 30 per cent of cases If all three tests had been carried out in every case, the percentage would have been higher

A fact of particular interest is that in 13 of the 26 cases examined increased F S H values were found and that despite this fact the œstrogen value in the 24-hour urine was lower than normal in 5 cases That there was no question of ovarian failure, however, was clear from the fact that in most of the latter cases an increased œstrogen value could be demonstrated either cytologically or histologically The apparent inconsistency thus depends on the differences, already mentioned, between the methods A high F S H production was no doubt responsible for the hyper-œstrogenism of the endometriosis patients Involvement of the hypophyseo hypothalamic system in the ætiology of endometriosis thus seems probable The disturbance in neuro-vegetative balance no doubt also originates from the same system and it *thus seems that endometriosis displays the characteristics of the* psycho-somatic disease group

The observations may be summarised as follows

Endometriosis patients were of average weight and were thus lighter than myoma patients Their blood pressure, however, was higher than the average, as is that of myoma patients Patients with pure endometriosis without myoma were comparatively young, the peak of their age distribution occurring ten years earlier than that of the patients with both endometriosis and myoma Histologically verified hyper-œstrogenism was commoner in the endometriosis with myoma group than in the pure endometriosis group, while cytological hyper-œstrogenism occurred in both On the other hand hyper œstrogenism as determined by biological assay of urine, was found in both groups In more than half of the patients who underwent the most thorough examination, hyper-œstrogenism was noted There were signs of hyper

œstrogens are the principal growth hormones affecting the endometrium Thus a combination of structural, neuro-vegetative and hormonal factors lead to the production of endometriosis

In the light of the present series, it appears that the somatic and neuro vegetative constitution of the patients plays an important role There is no doubt that the part played by the œstrogens varies It is obvious that even a normal œstrogen secretion is sufficient, provided that the other ætiological factors are strong enough On the other hand, a much increased œstrogen effect may, in a constitutionally less susceptible patient, lead to retrograde menstruation and so to endometriosis

The relation of endometriosis to parity has attracted continuous interest Although a considerable number of endometriosis patients are primarily sterile (Turunen, 1939 42 5 per cent, Philipp and Huber, 1940 45 per cent, Krokfors, 1959 66 7 per cent), there are among them a surprising number of women who have born children, a fact that argues against the theory of cervical obstruction

It is hard to believe that endometriosis arising directly after childbirth is always the result of retrograde menstruation due to cervical obstruction It seems more likely to be due to functional endocrine disturbance in connection with and as a sequel to, parturition Timonen and Krokfors, (1959) expressed the opinion that the reduction in size of the uterus during the period of lactation may cause the uterus to become functionally deficient in connection with the initial menses the condition resembling primary hypoplasia Vaginal smear specimens show that the first cycle after childbirth is often anovulatory and hyperœstrogenic The condition thus favours the occurrence of endometriosis

In the series examined cytologically there was more hyper œstrogenism than had been demonstrated histologically particularly in the pure endometriosis group This would indicate a relative surplus of œstrogens i e a reception deficiency due to an underdeveloped uterus When a normal quantity of œstrogens is not consumed there remains a relatively large quantity for the rest of the organism manifested for instance by a marked œstrogen reaction in the vagina Thus, since the uterus is obviously

cent of endometriosis patients Turunen (1939) found extreme hypoplasia of the uterus and in 15 5 per cent the menarche was later than normal (cf also Albrecht, 1955) In these patients, moreover, the frequency of various developmental disturbances was twice as high as average (Turunen, 1954)

In the present investigation it was unfortunately not possible to assess the degree of hypoplasia of the uterus On the other hand, information on the general constitution of the patients is available Their average height was slightly greater than that of the controls, their weight, however, being the same The systolic and diastolic blood pressures were clearly increased As compared with a previously published series of myoma patients, the endometriosis patients were lighter but in both series the blood pressure was higher than that of the controls, thus the endometriosis patients were of the same sympathicotonic neuro vegetative type as the myoma patients, although of more slender build

One of the present authors (Timonen and Purola, 1960) has investigated the relation between sympathicotonus and uterine motility In this field the experimental results are to some extent conflicting According to recent observations, however, it seems probable that the uterine motility is principally dependent on the noradrenalin content of the myometrium (cf Garret, 1954, 1956, Embrey, 1958) We may thus assume that the uterus of a sympathicotonic patient is over-sensitive to contraction stimuli It is therefore understandable that in a poorly developed hypoplastic uterus, or in a uterus in which there are some other factors that inhibit the correlation of contraction waves (e g myoma), retrograde menstruation would occur

If, furthermore, we consider the rather high frequency of hyper-œstrogenism in these patients, this becomes still more understandable It is well known that the motility of the uterus is dependent on œstrogens Posse (1958) was even of the opinion that the effect of œstrogens on the uterus is perhaps more easily detectable, and for a longer period, in the myometrium than in the endometrium He observed that rhythmic cycles of contractions may occur many years after the menopause Thus, the motility increasing effect of the œstrogens would combine with the neuro-vegetative component Nor should it be forgotten that

œstrogens are the principal growth hormones affecting the endometrium Thus a combination of structural, neuro vegetative and hormonal factors lead to the production of endometriosis

In the light of the present series, it appears that the somatic and neuro-vegetative constitution of the patients plays an important role There is no doubt that the part played by the œstrogens varies It is obvious that even a normal œstrogen secretion is sufficient, provided that the other ætiological factors are strong enough On the other hand, a much increased œstrogen effect may, in a constitutionally less susceptible patient, lead to retrograde menstruation and so to endometriosis

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the principal consumer of œstrogens its defective development is naturally reflected in the entire œstrogen metabolism, provided that the ovaries function normally

Such a reception deficiency implies weakness of the uterine circulation and also a variation of the œstrogen response both in the area of the endometrium, and also in that of the myometrium Deficient circulation during contraction results in anoxia, particularly if the contraction waves are not co ordinated and thus of little aid to the uterine circulation There is no doubt that most of the genital pain of patients with hypoplastic uteri and also part of the pain occurring in endometriosis arise in this way, as does the pain in the heart muscle in angina pectoris

It has been demonstrated (Timonen and Purola, 1960) that even strikingly large endometriotic foci do not cause pain if the patient has myomata Thus lack of pain would be explained by the good genital circulation characteristic of myoma patients In pure endometriosis, however, the situation is different Although, from time to time a surplus of œstrogens may occur, the uterus is not sufficiently well supplied with blood or functionally co ordinated It is possible that the results which have been obtained with œstrogen treatment of endometriosis can be explained along these lines by continuous administration of œstrogens the uterine circulation is gradually improved and its kinetic response to œstrogen becomes co-ordinated The circulatory deficiency of the uterus, as described above, also furnishes a natural explanation of the fact that, in endometriosis patients, premenstrual hyperæmia of the uterus is often absent (Turunen, 1939)

SUMMARY

A series of 381 endometriosis patients operated on during the period 1955 to 1958 at the Women's Clinic of the Helsinki University Central Hospital is presented Besides clinical data, endometrial specimens from 103 patients vaginal smears from 101 patients and urinary hormonal determinations (biological œstrogen, F S H and pregnandiol) were available

In 223 cases endometriosis occurred without myoma and in 158 with myoma (41 8 per cent) The peak of the age curve in

the former group was ten years earlier than in the latter, which is in keeping with the usual age of occurrence of myomata The average height and weight of endometriosis patients tallied with those of the controls Thus these patients were slimmer than myoma patients, who have been shown to be heavier and shorter than the normal subjects As in the myoma patients, however, the blood pressure was higher than that of the controls

Histological examination revealed endometrial hypoplasia in 40 per cent of cases Of these, 7 per cent occurred in connection with pure endometriosis and 33 per cent in connection with endometriosis with myoma Progestational changes in the endometrium were obserbveed in 30 per cent of cases

Judged by vaginal smears, increased œstrogen values occurred in 30 per cent of cases and when the specimen was taken at the end of the cycle in 60 per cent of cases Vaginal hyperœstrogenism was equally frequent in pure endometriosis and in the group of endometriosis with myoma

Urinary hormone determinations revealed increased œstrogen values ($\gtrsim$ 1000 IU) in 7 out of 26 cases Cytological hyper œstrogenism was present in 6 out of 15 of the same patients and histologically verified endometrial hyperplasia in 5 out of 9

Histological hyper œstrogenism determined on the basis of the hyperplasia of the uterine mucosa was commoner in the endometriosis with myoma group than in the group of pure endometriosis, while vaginal hyper œstrogenism was equally common in both This is ascribed to the fact that in pure endometriosis the uterus is hypoplastic and there is consequently a defect of the receptor mechanism

Constitutional deficiency (hypoplasia) combined with disturbed neuro vegetative balance is considered to be a primary factor in the ætiology of endometriosis For this reason the disease may occur at an early age Another factor is a comparatively increased œstrogen effect which in conjunction with the factors already mentioned results in uncoordinated uterine motility and so in retrograde menstruation After implantation moreover the œstrogens act as growth hormones

Both of the observed ætiological factors indicate a disturbance of the hypophyseo hypothalamic system

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THE ULTRASTRUCTURE OF THE EPITHELIAL CELLS OF THE ENDOCERVIX DURING THE MENSTRUAL CYCLE

BY

O NILSSON AND A WESTMAN

The cervical mucus originates from the glands of the endocervix and the uterine mucosa The physical properties of the mucus vary with the phases of the menstrual cycle and a number of attempts have been made to correlate these variations with concurrent morphological changes in the endocervical glands

Schroder (1930) failed to detect any cyclical changes in the glands According to Wollner (1942) the epithelial cells increase in height pre menstrually, when the epithelium desquamates Sjovall (1938) and Papanicolaou et al (1948) also found an increase in height of the lining cells but considered that maximal proliferation occurred at the time of ovulation Further studies of the cervical glands by conventional histological methods have shown morphological changes to occur but they were not sufficiently characteristic to permit their differentiation during the different phases of the menstrual cycle (Topkins 1949 Bradburn and Webb 1951 Duperroy 1951 Novak and Novak 1958)

Using histo chemical methods of examination Hedberg (1950) observed that the cellular content of alkaline phosphatase increased during the first part of the menstrual cycle Ortiz and Llusia (1955) confirmed this observation and also found that

the cells contained the largest quantity of secretion at the time of ovulation According to Atkinson *et al* (1948), Wheeler and Danziger (1955), and Gross and Danziger (1957) the endocervical glands do not undergo any constant cyclical changes

The presence of ciliated cells in the endocervical epithelium has been observed by Schroder (1930), Sjovall (1938), Bradburn and Webb (1951), and others Guillon (1944) expressed the view that mucus cells were transformed into ciliated cells during a period towards the end of the menstrual cycle This transformation of cells may be compared with that which, according to some authors, occurs in the rabbit Fallopian tube (for survey of the literature see Fredricsson, 1959)

A study of the structure of the endocervical glands, as revealed by electron microscopy, would probably contribute towards the better understanding of the cyclical changes in the cervical mucus The present electron microscopic study was therefore carried out to investigate (i) the ultrastructure of human endocervical mucosa, (ii) any changes which may occur during the different phases of the menstrual cycle

Case Material and Methods

The present series comprised 21 women of reproductive age on whom curettage was performed because of a history of infertility or metrorrhagia The patients in the latter group had been on the waiting list for a considerable time, during which the menstrual cycle had returned to normal and two or three menstrual periods had occurred prior to curettage

A small piece of endocervical epithelium was removed with a biopsy curette in 10 cases during the proliferative phase and in 11 cases during the secretory phase In all these cases light microscopy of endocervical mucosa revealed normal conditions The method of preparation of the curettings for electron microscopy was described in a previous paper (Borell *et al*, 1959)

Findings

Electron microscopy showed the endocervical glands to be lined with simple columnar epithelium which was separated from the stroma by a basement membrane

Three types of cell were identified (i) mucus cells, (ii) cells similar to the epithelial cells of the uterine body, (iii) ciliated cells The methods of examination used did not permit an assessment of the proportion of each type of cell which was present

Mucus cells The free surface of the mucus cells was seen to bulge into the glandular lumen (Figs 1, 2 4) In addition to secretory granules the apical part of the individual cells contained numerous small vesicles about 0 1 μ in diameter In some pictures the glandular lumen was connected with the vesicles and secretory granules through pore like openings in the cell membrane Numerous microvilli which varied in length arose from the surface of the cells The membranes between two adjacent cells showed desmosomes

The mucus cells contained a large number of secretory granules which were so abundant that they displaced the cytoplasm and its organelles (Fig 1) The Golgi apparatus was about 2 μ broad and a maximum of 8 μ in length It was well developed and seen in the form of parallel lines surrounded by circular structures of varying size (Fig 5) It was usually situated near the upper pole of the nucleus and lay nearly parallel with the nuclear membrane Spherical structures resembling those surrounding the Golgi apparatus were also seen in other parts of the cytoplasm predominantly in the apical part of the cell

The secretory granules were either lightly or darkly stained but transitional forms of greyish white colour were also visible

The *lightly stained secretory granules* predominated they were round about 1–2 μ in diameter and were enclosed in a membrane they were often so closely packed that their shape became irregular (Figs 1–5) Occasionally the limiting membranes had ruptured with resultant fusion of adjacent granules (Fig 4) The inner substance of the granules was usually homogeneous and only slightly electron dense Occasionally, it showed a few darker stained areas (Fig 1)

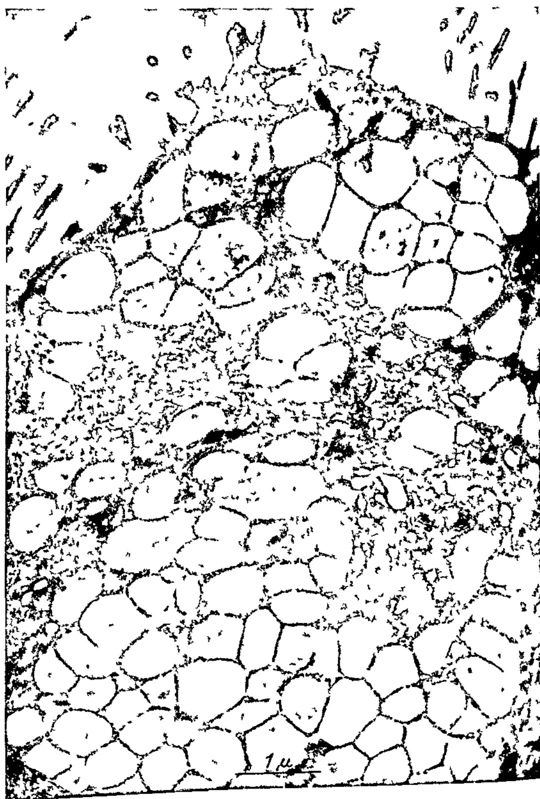


Fig 1



F g 2 Ap cal part of a mucus c ll of the endocerv cal ep thel um (prol fera ti e phase) Small es cles are v s ble n the cytoplasm below the surface of the cell Se eral l ghtly sta ned secretory granules are seen × 30 000

The *darkly stained secretory granules* were scanty they were round about 0 1–2 μ in diameter and were seen to be enclosed in a membrane (Fig 4) The smaller granules were often situated near the RNA membranes of the cells The electron density of some *granules varied Occasionally rod shaped granules were* identif ed which were about 1 μ broad and varied in length the longest being 4

F g 1 Part of a mucus cell of the endocerv cal ep thel um (prol ferati e phase) The cell conta ns a large number of closely approximated lightly sta ned secretory granules. These are n places separated from areas which are r h n cytoplasm and show n toc ondria the Golg apparatus and ot er cell organelles The ap cal surface of the cell bulges nto the glandular l men and possesses a large number of m cro lli × 19 000

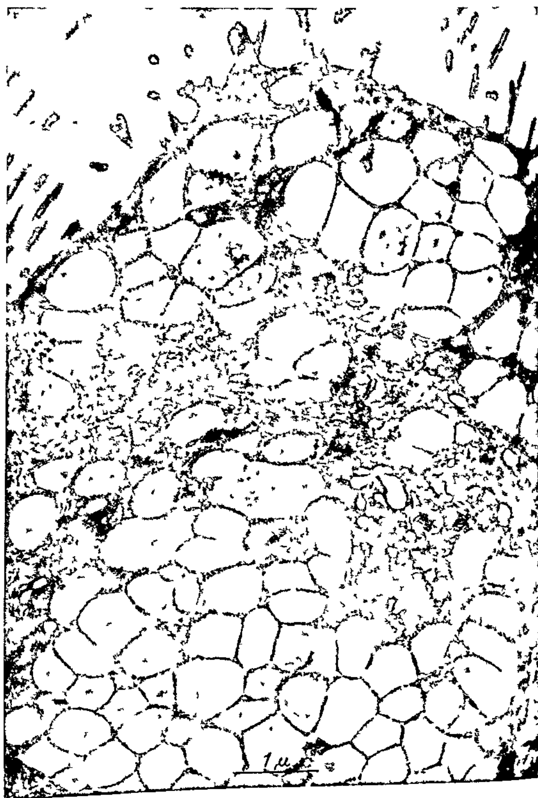
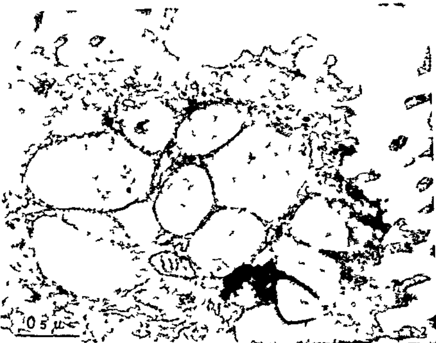


Fig 1



F g. 2 Ap cal part of a mucus c ll of the endocervical ep thel um (prolifera t e phase) Small ves cles are v s ble in the cytoplasm below the surface of the cell Several l ghtly sta ned secretory granules are seen × 30 000

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F g 1 Part of a mucus cell of the endocervical ep thel um (proliferative phase) The cell contains a large number of closely approximated lightly sta ned secretory gran les These are in places separated from areas which are ri h n cytoplasm and sl ow m tochondr a the Golgi apparatus and ot er cell organelles The ap cal surface of the cell bulges nto the glandular lumen and possesses a large number of m cro ill × 19 000



Fig 3

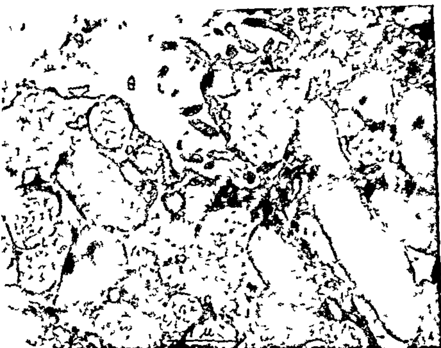


Fig 4 Apical parts of mucus cells of the endocervical epithelium (mid s cretory phase) The cell contains a large number of lightly-stained and darkly stained secretory granules Some of the lightly stained granules have coalesced A few darkly stained secretory granules are rod shaped × 23 000

The mucus cells did not undergo constant changes during the different phases of the menstrual cycle

The secretion discharged by the mucus cells of the endocervical epithelium appeared to pass to the lumen of the glands through openings in the cell membrane

The secretion present in the glandular lumen was seen as a homogeneous substance whose appearance was similar to that of the contents of the lightly stained secretory granules This secre

Fig 3 Part of a mucus cell of the endocervical epithelium (proliferative phase) Lightly-stained secretory granules surround a zone which contains cytoplasm and shows mitochondria and cytomembranes Small vesicles are seen between secretory granules × 46 000



Fig 3

Ciliated cells The ultrastructure of the ciliated cells was similar to that of the ciliated cell type occurring in other parts of the genital tract (Borell *et al* 1959) and did not undergo any cyclical changes

Cells showing both secretory granules and cilia were not observed

Discussion

The epithelium of the endocervix was found to contain three types of cell (i) mucus cells (ii) cells similar to the epithelial cells of the uterine body and (iii) ciliated cells The differentiation of these three types is easy if the apical part of the cells is visible in the electron microscopic picture However, if only small intracellular areas are seen differentiation may be impossible At the present stage of our knowledge, therefore, certain electron micrographs are difficult to interprete Thus no conclusions can be drawn concerning for instance the development of mucus cells

The mucus cells of the endocervical epithelium were found to contain three types of inclusions which are probably products of secretion These are small vesicles and lightly and darkly stained secretory granules The small vesicles probably originate near the Golgi apparatus from the Golgi membranes (Nilsson 1959) The origin of the lightly stained and darkly stained secretory granules is still unknown The view has been expressed that both the RNA membranes and the Golgi apparatus are concerned in the formation of the secretory granules in different types of cell (Pipan 1960 Florey 1960 and others)

The simultaneous occurrence of lightly stained and darkly stained granules in secretory cells is rather common Several authors consider one type of granule to be the precursor of the other (Rhodin and Dalhamn 1956 Nilsson and Rutberg 1960) Rhodin and Dalhamn (1956) in goblet cells found certain intermediary forms to occur in the conversion of dark secretory granules into light ones The mucus cells in the endocervical epithelium also contained granules which appeared to be intermediary forms between dark and light granules However the

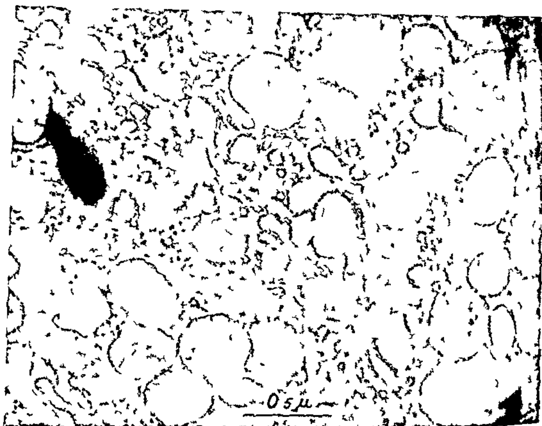


Fig 5 Golgi apparatus from a mucus cell of the endocervical epithelium (secretory phase) The membranes and vesicles of the Golgi apparatus are surrounded by lightly stained secretory granules × 44 000

tion contained darkly stained secretory granules and cell fragments

Cells similar to the epithelial cells of the uterine body The ultrastructure of the cells of the uterine epithelium and the cyclical changes which they undergo were described by Borell *et al* (1959) A cell similar to this type of cell was also found in the endocervix and cyclical changes were observed here also During the proliferative phase the cytoplasm contained granules and numerous RNA membranes the surface of the cells was studded with microvilli of considerable length During the secretory phase the cells contained numerous small vesicles and showed lightly stained zones which probably represented glycogen The surface of the cells showed fluffy processes

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differences in colour might have been due to differences in the thickness of the sections Each of these two types of granule probably represents an individual product of secretion The rod shape of some darkly-stained granules and the occurrence of darkly stained granules in the secretion of the glandular cells support this view

The secretion of the endocervical glands appears to be composed of the contents both of the lightly-stained secretory granules and of the vesicles present in the apical part of the cells Further constituents are darkly-stained secretory granules, cell fragments and probably material capable of penetrating the cell membrane The methods used did not disclose any changes in the ultrastructure of these constituents during the menstrual cycle

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Electron microscopy of human endocervical epithelium revealed the following three types of cell (i) mucus cells, (ii) cells similar to the epithelial cells of the uterine body, (iii) ciliated cells Secretory cells possessing cilia, were not identified

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No changes in the morphology of the mucus cells were observed during the menstrual cycle The cells similar to those of the epithelial cells of the uterine body showed cyclical changes but such changes were not observed in the ciliated cells

Acknowledgement

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Kullander Stig and Kallén Bengt Acta obst et gynec Scandinav 40 -34, 1961
From the Department of Gynaecology (Professor Alf Sjövall) and the Department of Embryology University of Lund, Sweden

THE FIBRINOLYTIC ACTIVITY OF HUMAN ENDOMETRIUM, STUDIED IN TISSUE CULTURE

Part II Carcinoma of the Uterine Body

BY

STIG KULLANDER AND BENGT KALLÉN

Studies of human endometrial carcinoma kept in tissue culture seem to be a possible approach to an analysis of some of its biological properties Few such studies appear in the literature Maccabruni (1914) published a few drawings of epithelioid growth from a uterine tumour in tissue culture and stressed the fibrinolytic properties of the cells He mentioned that plasma obtained from pregnant donors reduced the fibrinolytic activity of the tissue Moore (1956) described good growth from a primary carcinoma taken from a 56-year old patient A stronger growth was obtained than from normal endometrial specimens Papanicolaou and Maddi (1958) described with photographs three cases of uterine carcinoma In one case, an adenocarcinoma, a cell mat of epithelial cells developed In another, a papillary carcinoma, a picture of papillary fronds was seen In the third case, a carcino sarcoma, abundant growth of malignant epithelial and stromal cells occurred

In the present paper the results of tissue culture of human endometrial cancer are described the outgrowth pattern and the fibrinolytic properties of the tumours *in vitro* are considered Investigations into the influence of hormones on growth and fibrinolytic activity are now in progress

Table I *Human Uterine Body Carcinoma Studied in Tissue Culture*

Specimen Number	Age of Patient	Pat. anat Grading	Type of Outgrowth Pattern	Type of Fibrinolysis	LT	
					Control	LEe
1	73	I	II	A	3 –	5 5
2	70	IV	—	A	2 +	3 —
3	73	VI	III	B	> 14	> 14
4	63	IV	II	B	8 5	11
5	66	IV	I	A	4 —	6 –
6	54	IV	I	C	3	14
7	54	I	I	C	- +	?
8	82	III—IV	III	A	3 +	3
9	64	IV	IV	B	13	13 5
10	61	I	I	C	2 5	13 5
11	59	I	I + IV	A	- 5	4
12	64	IV	—	A	1 5	2 5
13	68	IV	II	A	- 5	2 5
14	79	IV	II	B	14	~
15	56	II—III	I	B	6 +	8 5
16	75	IV	III	A	4 5	7 5
17	70	III	I	B	> 14	> 14
18	47	IV	IV	A	3 5	6 5
19	58	IV	III	A	4 5	5
20	41	III	I	A	- 5	3 5
21	61	III	I	A	2 5	5 5

Material and Methods

In a previous paper by the present authors (1961) a study of normal human endometrium in tissue culture was described The methods used in that study are the same as those used in the present investigation Tissue cultures have been prepared from cancer specimens obtained at curettage using plasma clot cultures in Carrel flasks In control cultures the clots consisted of equal parts of cockerel plasma and chick embryo extract diluted with Tyrode to 5 per cent in LEe cultures lysin ethyl ester was added to a final concentration of 2 5 mg /ml As a fluid phase adult human serum was used Streptomycin and penicillin (50 units ml of each) was added to combat infection which was therefore never a serious problem

Kullander Stig and Källén Bengt Acta obst et gynec Scandinav 4? -34, 1961

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Fig 1 Phase-contrast micro-photograph of cells growing out from a human uterine body carcinoma Case No 15 Growth resembling that from normal endometrium (growth pattern I) × 320

a fact which was also reflected by the presence of large nucleoli in the cells Among the outgrowing cells atypical cells could also often be seen A picture of such a growth pattern is shown in Fig 1

Group II In these cases the epithelial outgrowth pattern dominated The single cells were relatively large but their size varied considerably and many intracellular inclusions and degeneration phenomena were present Also nucleoli were large and multi

Results

In Table I, a summary of the different tumours studied is given with their histological grading, outgrowth pattern, and fibrinolytic activity

The histological grading of the tumours was performed by Professor Santesson, according to a modification of Reuterwall's (1941) system

Pattern of Cellular Outgrowth

A description of the cellular outgrowth from normal endometrial tissue in various stages of the endometrial cycle and in senile involution was given previously (Kullander and Kallen, 1961) The outgrowing cells are mainly epithelioid but relatively polymorphic even in senile endometrium In the latter, however, epithelial outgrowth is less pronounced as compared with fibroblastic growth

The cell growth pattern in cultures prepared from carcinoma of the uterine body varies greatly Different cancer specimens showed distinct patterns of growth, and in some cases a marked variation in cellular appearance was also seen in different cultures prepared from the same cancer specimen, a fact easily explained by the great variation in histological appearance between different parts of one tumour

The presence of fibrinolytic processes, which will be further discussed later, also influenced the cellular growth pattern Only in 2 cases was the fibrinolysis so marked that no cellular outgrowth could be found, but in most cases the cell sheets formed were rapidly broken up and disfigured by plasma digestion In some cases, however, vividly growing cell sheets were seen after the complete destruction of the central explant

Different patterns of growth could be seen in cultures of different tissue specimens The following four types are rough subdivisions – intermediate and mixed forms were abundant

Group I In this group a cellular arrangement was seen strongly resembling that of a normal senile endometrium with a large stromal component The growth activity however was greater



Fig 3 Phase-contrast micro-photograph of cells growing out from a human uterine body carcinoma *Case No 19 Small epithelial cells with large nucleoli* and sometimes two nuclei (growth pattern III) × 320

with a strong tendency to form cell beams An example is shown in Fig 4

If these outgrowth patterns are compared with the histological structure of the biopsies an obvious source of error is the large variation between different portions of the same tumour In an attempt to avoid this large specimens of the tumour were taken and fixed immediately for histological examination while a small piece was also taken for histology directly adjacent to that used for culture



Fig 2 Phase-contrast micro photograph of cells growing out from a human uterine body carcinoma Case No 14 Large epithelial cells with numerous vacuoles and signs of degeneration (growth pattern II) × 320

nucleation was frequently seen A picture of such a specimen is shown in Fig 2

Group III In these cases too the epithelial growth dominated but the cells were smaller, their individual sizes varied less and their growth was much stronger Large nucleoli and abundant intra cellular inclusions were the rule Degenerative signs were seen less frequent An example is given in Fig 3

Group IV In a few cases an extremely small celled immensely rich outgrowth was seen, probably of epithelial character,



Fig 3 Phase-contrast micro-photograph of cells growing out from a human uterine body carcinoma Case No 19. Small epithelial cells with large nucleoli and sometimes two nuclei (growth pattern III) × 320

with a strong tendency to form cell beams An example is shown in Fig 4

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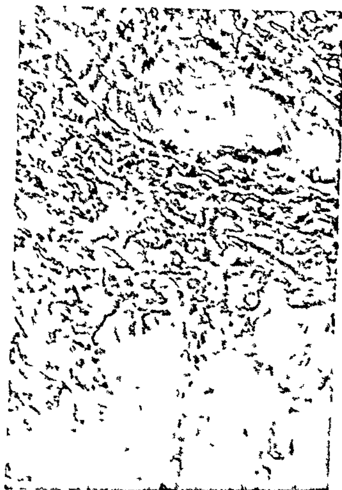


Fig 4 Phase-contrast micro-photograph of cells growing out from a human uterin body carcinoma, Case No 9 Densely packed small cells of apparently epithelial nature There is a strong tendency to cell beam formation (growth pattern IV) × 320

In 3 cases the histological examination revealed a papillary carcinoma One of these grew according to growth pattern I, one according to growth pattern II, and one showed a mixture of patterns I and IV

In 4 cases the carcinoma showed a highly differentiated adeno carcinoma structure (Reuterwall's Groups II and III) All of these grew according to growth pattern I

In 12 cases the degree of differentiation was intermediate ac

cording to Reuterwall s grading system (his Group IV) Two of these grew according to pattern I, 3 according to pattern II, 3 according to pattern III, and 2 according to pattern IV Due to strong fibrinolysis, 2 showed no outgrowth.

One case showed little differentiation histologically, a large part being solid (Reuterwall's Group VI) Its growth pattern was of Type III

There is, thus, little agreement between the histological structure of the carcinoma and its growth pattern *in vitro* We have not been able to verify the observation of Papanicolaou and Maddi (1958) of a difference in growth pattern between papillary adenocarcinoma and other types

The most characteristic feature of growth pattern I was the considerable intermingling of stromal cells Stromal growth was less marked in Groups II to IV An attempt was made to discover if difference in age affected the growth pattern The mean age of patients with carcinoma growing according to pattern I was 58 0 years with a standard error of 2 77 years that of patterns II to IV was 68 2 years with a standard error of 3 33 years A t test between these means gives $t = 2\ 3$ at 17 d f, $0\ 02 < P < 0\ 05$

Fibrinolytic Activity in vitro

The fibrinolytic activity *in vitro* of the different tumours was judged according to the method previously used by the present authors (1961) Thus the time necessary for a detachment of half of the explants from one tumour specimen was determined and called LT LT_{50} was compared in control cultures and in cultures prepared with LEe in the clots in order to judge the release of plasmin activators

According to this standard three types of tumours could be distinguished (cf also Table I)

(A) In this type represented by 12 cases the control LT_{50} time was short (less than 5 days) and the lengthening of LT_{50} obtained by addition of LEe was nil or slight (maximum 3 days)

(B) In this type represented by 6 cases a long LT_{50} time was obtained in control cultures The addition of LEe did not result in any marked reduction of the fibrinolytic activity

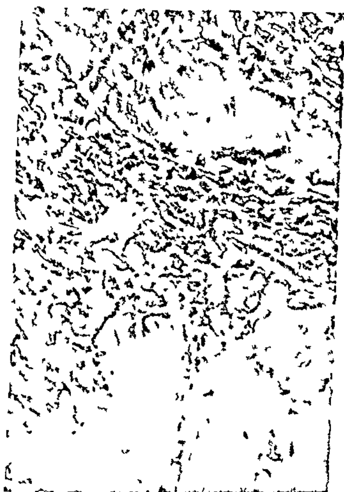


Fig 4 Phase-contrast micro photograph of cells growing out from a human uterin body carcinoma Case No 9 Densely packed small cells of apparently epithelial nature There is a strong tendency to cell beam formation (growth pattern IV) × 320

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In 12 cases the degree of differentiation was intermediate ac

in control cultures was much lower (Type B), and no further reduction was seen after addition of LEe, less proteolytic enzyme was probably released in those cases In a further 3 cases the fibrinolytic activity in control cultures was comparable to those of type A, but addition of LEe resulted in a great reduction of the fibrinolysis (Type C) We regard these tumours as releasing a high amount of activators of plasminogen

The different fibrinolytic activity *in vitro* of different tumours is comparable to the results obtained by the present authors in normal endometrial tissue at different stages of the endometrial cycle There are no indications in the present series of differences in activity between different kinds of carcinoma

SUMMARY

Twenty one cases of human endometrial carcinoma have been successfully cultured *in vitro*

Four different growth patterns were found One of these is characterized by strong stromal activity It generally occurred in tumours taken from younger patients than did the other growth patterns No significant correlation between growth pattern and histological structure of the tumour was observed

Most tumours showed a strong fibrinolytic activity *in vitro*, probably due to release of proteolytic enzymes In only 3 cases fibrinolytic activity occurred that could be interpreted as a release of activators of plasminogen No significant correlation between growth pattern, histological differentiation and fibrinolytic activity could be found

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The cost of this investigation was defrayed by the Swedish Cancer Society

(C) In this type, represented by 3 cases, the control LT_{60} time was as short as in Group A, but the addition of LEe resulted in a marked lengthening of LT_{60}

The present series did not suggest any correlation between the pattern of outgrowth and the type of fibrinolytic activity

Table II *Fibrinolytic Activity*

		Type of Fibrinolysis		
		A	B	C
Type of outgrowth	I	4	2	2
	II–IV	6	3	0

Furthermore, no significant difference in the age of the patients was found between patients with carcinoma of differing fibrino lytic activity *in vitro* The mean age for Group A was 63 7 years with a standard error of 3 34 years, that of Group B was 67 5 years with a standard error of 3 33 years, and that for Group C was 56 7 years with a standard error of 2 35 years An F test gave a value of $F = 1\ 22$ for $n_1 = 2$ and $n_2 = 18$ The probability of these means belonging to the same population is thus $> 0\ 05$

Discussion

Good growth was obtained in plasma clot cultures of human endometrial carcinoma In one group the growth picture was dominated by stromal growth, epithelial cells were, however, intermingled and showed signs of a high growth activity This growth pattern was seen in all histological types of carcinoma This picture was seen more in specimens from relatively young patients with carcinoma

The cancer cultures show a strong fibrinolytic activity in most cases Three different types of fibrinolysis could be distinguished Among the 21 cases investigated, 12 showed strong fibrinolysis in control cultures, and addition of LEe gave rise to little or no re duction of the fibrinolytic activity (Type A) We interpret this result – in accordance with the previous discussion (1961) as a sign of a strong release of proteolytic enzymes, unrelated to the system activating plasminogen In 6 cases the fibrinolytic activity

Case Series

The case series comprised 87 women in various stages of pregnancy. Forty six of these patients were apparently healthy and constituted the normal cases. Eleven were admitted to the hospital due to Rh sensitization and 30 suffered from pruritus of pregnancy.

Besides routine clinical and laboratory examinations all patients were either questioned or sent a questionaire with special reference to itching during the present pregnancy, as well as previous history of icterus, gall bladder or liver disease. Patients with pruritus of pregnancy exhibited generally only slight itching, which in most cases appeared at the 6th or 7th month of gestation and disappeared after delivery. The normal and Rh sensitized cases denied all symptoms of itching. The Rh sensitized women usually had high Rh titers and their infants exhibited severe signs of erythroblastosis fœtalis.

Blood samples for the determination of S OCT were taken from the patients on admission to hospital (third trimester) or on their visit to the Clinic (first and second trimester). In those cases where blood was drawn both from the mother and from the fœtus (umbilical vein) the samples were taken at the same time to compare maternal and fœtal S-OCT levels.

Ornithine carbamyl transferase activity. OCT in tissue homogenates and body fluids was determined by the method of Reichard and Reichard (1958). Results were expressed in micromoles of $^{14}CO_2$ liberated by 1 g tissue or 1 ml body fluid under standard conditions. However in the case of serum (S-OCT) as in previous papers the unit is given per 0.5 ml.

Preliminary normal values for non pregnant women are ≦ 0.05 μM $^{14}CO_2$ per 0.5 ml serum (Reichard 1960).

Results

Tissue homogenates and body fluids. As seen from Table I all normal maternal and fœtal tissues and body fluids examined showed low OCT as compared to liver (Reichard 1960).

S OCT in normal pregnancy. Blood serum was obtained from

Reichard Hans Wiqvist Nils and Yllner Sven Acta obst et gynec. Scandinav [illegible] *-44 1961*

From King Gustaf V Research Institute (Professor G Birke) the Department of Internal Medicine (Professor H Lagerlof), the Department of Women s Diseases (Acting Professor N E Pahlsson), Karolinska Sjukhuset, and the National Institute of Public Health, the Department of Industrial Health (Professor A Ahlmark), Stockholm, Sweden

SERUM ORNITHINE CARBAMYL TRANSFERASE ACTIVITY IN NORMAL PREGNANCY AND IN PREGNANCY COMPLICATED BY PRURITUS

BY

HANS REICHARD NILS WIQVIST AND SVEN YLLNER

The determination of serum ornithine carbamyl transferase activity (S-OCT) has been found to be a sensitive test for demonstrating liver disease (Reichard, 1957, 1961, Brown and Grisolia, 1959, Moretti *et al*, 1960, Šmahel and Rysanek, 1960) *The aim of this study was to investigate S OCT in healthy* pregnant women and in patients with pruritus of pregnancy In addition S-OCT was determined in a few cases of Rh sensitized women and infants with erythroblastosis fœtalis

Material and Methods

Tissue homogenates The tissue homogenates shown in Table I were prepared from samples obtained by Cæsarean section on women *The pieces of tissue were immediately frozen and stored* The subsequent procedures were carried out at 0° C The samples were thoroughly homogenized with 9 parts of distilled water in a Waring blendor for 4–5 minutes After homogenizing the samples were immediately incubated for the assay of ornithine carbamyl transferace activity (OCT)

Table II Maternal and Fœtal Serum Enzyme Activity (S-OCT) at Term

Case		S-OCT in μM $^{14}CO_2$ per 0.5 ml. Serum	
		Maternal	Fœtal
Pruritus			
	B L.	0 096	0 023
	B A.	0 729	0 026
	S O	0 050	0 010
	M. L.	0 165	0 016
Rh sensitized			
	I J	0 205	0 010
	E K.	0 014	0 026
	M M.	0 041	0 003

S-OCT was determined in 29 women during the third trimester S OCT less than 0 05 was found in 25 cases, between 0 05 and 0 1 in 3 cases and more than 0 1 μM $^{14}CO_2$ in 1 case (Fig 1)

S OCT in Rh sensitized women Nine out of 11 Rh sensitized women in the third trimester showed S-OCT less than 0 05, 1 case between 0 05 and 0 1, and 1 case more than 0 1 μM $^{14}CO_2$ (Fig 1)

S OCT in pruritus of pregnancy This group included 30 patients in the third trimester of pregnancy Routine liver tests were not performed in all patients Visible jaundice was however, observed in only 2 out of 30 women with pruritus of pregnancy Six patients with itching exhibited an enzyme activity of less than 0 05 10 cases between 0 05 and 0 1, and 14 cases more than 0 1 μM $^{14}CO_2$ (Fig 1)

Comparison between maternal and fœtal S OCT As seen from Table II S-OCT was low in cord blood both in cases with erythroblastosis fœtalis and in cases with pruritus of the mother although maternal S OCT in three of these latter patients was elevated

Discussion

In man OCT occurs chiefly in the liver and in small quantities also in the small intestine In all other tissues examined very low OCT levels were found (Reichard 1960) All tissues and body fluids from the female genital tract and fœtuses examined in the

Table I *Enzymatic Activity (OCT) in Different Tissues and Body Fluids from Pregnant Women and Fœtuses*

Organ or Body Fluid	No. of Samples	OCT in µM $^{14}CO_2$ per 1 g Tissue or 1 ml. Body Fluid	
		Mean	Range
Myometrium	3	0 98	0 24 – 1 48
Decidua	2	0 08	0 08
Maternal blood serum	29	0 064	0 020 – 0 210
Umbilical cord	4	0 19	0 10 – 0 42
Fœtal membranes	4	0 09	0 06 – 0 14
Placenta	4	0 06	0 04 – 0 08
Cord blood serum	6	0 052	0 020 – 0 112
Amniotic fluid	3	0 005	0 002 – 0 006

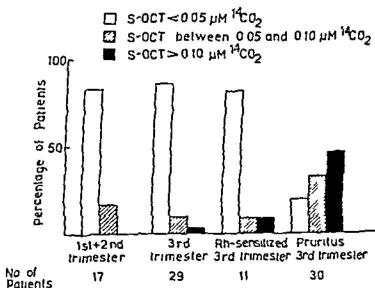


Fig 1 S OCT in normal pregnancy, in Rh sensitized women, and in patients with pruritus of pregnancy

17 patients in the first and second trimester, 14 of these cases showed S OCT values less than 0 05 and 3 values between 0 05 and 0 1 µM $^{14}CO_2$ per 0 5 ml serum (Fig 1)

Jaundice of pregnancy was followed by itching in 85 per cent of Thorlings (1955) cases On the other hand pruritus of pregnancy is often associated with jaundice Arfwedson (1955) demonstrated that 65 per cent of 100 cases with itching during pregnancy showed serum bilirubin values above 1 mg per cent, whereas the corresponding value in normal pregnant women was 6 per cent Thus pruritus of pregnancy may be regarded as an early symptom of disturbed liver function (Thorling, 1955)

As S-OCT elevation is observed both in cases with obstruction of the biliary ducts and in parenchymatous disease (Reichard, 1960), the ætiology of the liver disturbance in pruritus of pregnancy can not be elucidated on the basis of elevated S OCT

The low S-OCT of fœtal cord blood in normal cases indicates that the S OCT in newly born children is of the same magnitude as in adult blood Regarding other enzyme activities the S-GOT S GPT alkaline phosphatase activity lactic dehydrogenase activity and aldolase activity have been reported to be elevated in fœtal blood serum (Lapan and Friedman 1959 Pojerova and Tovarek 1959 Christiansson and Josephson, 1960 Persson 1960)

In the present investigation no parallel between the S-OCT of the mother and the fœtus could be demonstrated (Table II) It seems likely therefore, that the placenta constitutes a barrier for OCT

Jaundice in erythroblastosis is of hæmolytic origin but may be associated with hepatic dysfunction It may be that the liver function in these infants is disturbed possibly due to the increased functional requirements of conjugating and excreting the degradation products of hæmoglobin Decreased serum levels of cholinesterase activity in such cases (Bleisch and Schwachman, 1954 Brody 1960) seem to indicate disturbed liver function The normal S OCT in our cases indicate that this assumed hepatic dysfunction is not associated with hepatic cellular injury

SUMMARY

Ornithine carbamyl transferase activity (OCT) was determined in tissue homogenates from the genital tract of pregnant women,

present investigation, showed OCT levels below 1 μM ^{14}CO per 1 g tissue or 1 ml fluid These figures are very low compared with those obtained from the liver, being 2,500 μM ^{14}CO (Reichard, 1960) Our findings therefore imply that damage to these tissues is unlikely to influence the S OCT significantly

The serum activity of glutamic oxalacetic transaminase (S GOT), glutamic pyruvic transaminase (S GPT) (Wroblewski *et al*, 1956) as well as that of S-OCT (Reichard, 1957, 1961, Brown and Grisolia, 1959, Moretti *et al*, 1960, Šmahel and Ryšanek, 1960) have been found to be sensitive tests for liver cell injury These new enzymatic tests have therefore been employed to study the occurrence of liver disturbances during pregnancy In normal pregnancy, labour, and puerperium normal S-GOT and S-GPT levels were reported by Borglin (1958, 1959), Johansson *et al* (1958), Kokot *et al* (1958), Persson (1959, 1960), Normann *et al* (1960), and others Elevation of S-GOT on the first day after parturition was, however, observed by Reichard *et al* (1960) Occasionally elevated S OCT in normal pregnancy was reported by Normann *et al* (1960) and these findings were confirmed by Reichard *et al* (1960)

In the present study S-OCT was elevated in 7 out of 46 normal pregnant women, *i e* in approximately 15 per cent Almost the same distribution was found in Rh sensitized women (Fig 1) In 30 patients with pruritus of pregnancy, 24 (80 per cent) exhibited elevated S-OCT (Fig 1) The close connection between pruritus of pregnancy and elevated S-OCT suggests liver cell damage in these cases

There are different opinions as to the pathogenesis of jaundice in pregnancy Genuine jaundice of pregnancy is characterized by a normal thymol flocculation test and by a greater elevation of alkaline phosphatase activity than seen in normal pregnancy (Thorling, 1955 Hoynk van Papendrecht, 1957, Wetstone *et al*, 1958) Caroli (1954) found bile thrombi in liver biopsies from patients with jaundice of pregnancy Svanborg (1954) suggested that this type of icterus was due to disturbed motility of the bile ducts and Thorling (1955), in his extensive study, concluded that the causative mechanism was an *incomplete intrahepatic biliary obstruction*

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from various fœtal tissues and amniotic fluid In all samples investigated low enzyme activity was found which implies that damage to these tissues is unlikely to influence the serum level of OCT (S-OCT)

S-OCT was determined in 46 healthy women in various stages of pregnancy and was found to be slightly elevated in 7 (15 per cent) Almost the same distribution was observed in 11 Rh sensitized women Of 30 patients with pruritus of pregnancy, however, the S-OCT was elevated in 24 (80 per cent) and this elevation was marked in 15 (50 per cent) This indicates a close connection between pruritus of pregnancy and hepato-cellular disturbance

Low S-OCT was recorded in cord blood from infants with erythroblastosis due to Rh-sensitization of the mothers This suggests that the liver in these infants was not affected to such an extent as to cause a release of OCT to the blood

Addendum

S-OCT was determined in 222 healthy men and non pregnant women and was found to be less than 0 030 $\mu M^{14}CO_2$ in individuals younger than 25 years, and less than 0 060 $\mu M^{14}CO_2$ in individuals older than 25 years (Reichard, H, to be published)

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The abnormal response to tryptophan loading in pregnancy can be overcome by an increased intake of pyridoxine (Wachstein and Gudaitis, 1952, 1953 a, Zartman et al 1955)

In pregnancy there is probably an increased demand for vitamin B_6. Vitamin B_6 was recommended for the treatment of nausea and vomiting of pregnancy as far back as 1942 on a purely empirical basis (Willis et al, 1942) Evidence for a relative pyridoxine insufficiency in this condition was presented in 1949 by McGanity et al, who showed that subjects with hyperemesis gravidarum exhibit an abnormal response of blood urea levels following the administration of alanine which could be corrected by administration of pyridoxine

Using paper chromatographic methods Wachstein and Lobel (1954) could demonstrate the occurrence of abnormal tryptophan metabolites in the urine of pregnant women after tryptophan loading The abnormal excretion pattern was strikingly similar to that described in vitamin B_6 deficient rats (Dalgliesh, 1952) Moreover following the administration of pyridoxine the excretion pattern approximated to that of normal, non pregnant controls

According to Turner and Reynolds (1955) the concentration of the main excretory product of pyridoxine in the urine, 4-pyridoxic acid is not diminished during pregnancy but Beaton et al (1951) found it to be significantly lowered. Applying a vitamin B_6 load test Wachstein and Gudaitis (1953 b) could demonstrate a significantly greater retention of ingested vitamin B in pregnancy as compared to the non pregnant state

It is widely accepted that the components of vitamin B_6 act as a co-enzyme for one or more transaminases In B_6 deficiency the blood transaminase activity is low (Marsh et al 1955) However, the glutamic oxalacetic transaminase activity and the glutamic pyruvic transaminase activity are found to be the same in pregnant as in non pregnant women (Glendening et al, 1955 Borglin, 1959 Borglin and Falk 1959 Persson 1959 1960 Dubach and Stamm 1958 Sprince et al 1951 Page and Brown 1952 Page 1956)

Diding Nils Å and Melander Stig E J Acta obst. et gynec. Scandinav [illegible] 1961

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SERUM VITAMIN B_6 LEVEL IN NORMAL AND TOXÆMIC PREGNANCY

BY

NILS Å DIDING AND STIG E J MELANDER

The suggestion has been made that pregnant women are deficient in vitamin B_6* due to dietary inadequacies or to the demands of the growing fœtus which drains the maternal system of this vitamin The supposed deficiency of vitamin B_6, which it is rarely possible to detect clinically in normal pregnancy, has been demonstrated mainly through the tryptophan load test Following the ingestion of tryptophan, normal individuals excrete only small amounts of xanthurenic acid in the urine while in B_6 deficiency the excretion is markedly increased (Lepkovsky *et al*, 1943, Greenberg *et al*, 1949, Glazer *et al*, 1951)

Sprince *et al* (1951) were the first to apply the tryptophan load test to normal non pregnant women and to women in the last trimester of pregnancy Using morning specimens of urine they could demonstrate a high concentration of xanthurenic acid in toxæmia while in uncomplicated pregnancy the excretion was not different from that of normal controls Using 24 hour specimens of urine Wachstein and Gudaitis (1952, 1953 a), however, could demonstrate a high excretion also in uncomplicated pregnancy and these results have been confirmed by Zartman

* In this communication by vitamin B_6 we mean the B_6 complex including pyridoxine, pyridoxal, and pyridoxamine

Saccharomyces carlsbergensis while Boxer *et al* (1957) deter mine pyridoxal-5 phosphoric acid, the active co-enzyme form of the vitamin

Diding (1955) presented a simple method for microbiological assay of the vitamin B_6 complex in pharmaceutical preparations We have studied the applicability of this method to the assay of vitamin B_6 in human blood This communication deals with the results obtained in determinations of B_6 in the serum of healthy non pregnant male and female human subjects, and in women with normal and toxæmic pregnancies This seems to be the first report on vitamin B_6 blood levels during gestation in humans The results of loading tests are also given

Material and Methods

The series comprised 5 healthy, fertile men 18 healthy women in the reproductive age group with normal menses 26 women in the last trimester of an uncomplicated pregnancy, and 10 women with toxæmia of pregnancy In 7 of the men and non pregnant women pyridoxine loading tests were performed with subsequent determination of blood levels

The men and non pregnant women were medical students and nurses The pregnant women were either attending the Ante natal Section of the Clinic or were in hospital

No records were made of the diet of the patients It is however, assumed that the Swedish diet contains a fairly high vitamin B_6 content (see Borglin and Falk, 1959)

Most of the pregnant patients received commercial multivitamin tablets The amount of pyridoxine in these tablets is declared to be 2 mg As a rule 6 mg pyridoxine per day was administered to the patients in this way

No close determination of the menstrual phase was made but the date of the last menstruation was recorded and thus the probable endometrial phase could be calculated

The length of the pregnancy was determined from the first day of the last normal menstruation and was checked by the findings at obstetrical examinations the actual date of delivery and the weight of the baby

Data pointing to an increased demand for vitamin B_6 in toxaemia of pregnancy are few Sprince *et al*, (1951) found the excretion of xanthurenic acid to be higher in toxaemia as compared to normal pregnancy whereas Wachstein and Gudaitis (1953 b) found no significant difference in xanthurenic acid level between toxæmic and normal pregnancies

As may be seen the evidence that pregnancy usually produces a conditioned deficiency of, or an increased demand for, vitamin B_6 is inconclusive It seemed that direct estimation of the blood level of vitamin B_6 might solve the problem Data on blood levels in man are, however, few and scanty Marsh, Greenberg, and Rinehart (1955) have reported blood levels of total vitamin B_6 complex in men and non pregnant women to be in the range of 0 017 to 0 018 microgram per ml of whole blood with a rise to about 0 085 microgram per ml on a pyridoxine intake of 15 mg per day Friedman *et al* (1955) and Vilter *et al* (1954) in short communications state that they found no significant difference in levels of vitamin B_6 in 'blood' from pregnant and non pregnant women but it is difficult to judge the value of their work because no numerical values or other experimental figures are presented and the method of assay is not mentioned In a review, Vilter (1956) gives the average figure of 0 050 microgram per ml 'blood' for vitamin B_6 and pyridoxalphosphate one-tenth this amount He presents no other data The method of assay is not described nor is it stated whether the subjects were pregnant or non pregnant Boxer *et al* (1957) report determinations of pyridoxalphosphate in whole blood from non pregnant subjects In 113 adult persons they found in the majority of the cases that the amounts were too small to be detected by the method used Only 11 of the subjects showed 0 010 microgram per ml or more The highest value observed was 0 037 microgram per ml

Several methods have been proposed for the assay of vitamin B_6 and for a detailed description of these methods and their limitations the reader is referred to reviews (Vilter, 1956, Diding, 1955) Methods hitherto published on the assay in blood are few Only two methods have been found in the literature Greenberg and Rinehart s in 1949 consists of an extraction of B_6 from blood with subsequent determination with the microorganism

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Table II *Loading Tests*

Amount per Os	Microgram Vitamin B per ml. Serum	
	Before Administration	After Administration (Hours)
20 mg	0 03	0 18 (2 hours)
20 mg	0 03	0 19 (2 hours)
20 mg	0 03	0 18 (2 hours)
60 mg	0 03	0 69 (2 hours)
80 mg	0 09	0 13 (1 hour)
100 mg	0 06	1 50 (3 hours)
250 mg	0 05	2 30 (3 hours)

The mean ± S D for man was 0 037 ± 0 003, and for the total of women 0 028 ± 0 043 microgram/ml This difference is not statistically significant (P> 0 8) The values for the calculated proliferative and secretory menstrual phases were 0 030 respectively

The mean ± S D for the pregnant, healthy women was 0 033 ± 0 034 microgram/ml It is obvious that there is no significant difference between the values for pregnant and non pregnant subjects The corresponding values for the toxæmic women was 0 025 ± 0 035 microgram/ml The difference between the means in toxæmia and uncomplicated pregnancy is not statistically significant (P> 0 5)

According to the primary figures there was no significant difference between mild and severe pre eclampsia (0 010 and 0 040 microgram/ml respectively) Also no correlation could be obtained between week of gestation and serum level

Loading Tests

The serum level of vitamin B_6 was also determined in seven healthy individuals before and after oral administration of pyridoxine The results are shown in Table II

The mean in this group before administration was 0 033 microgram/ml and increased to 0 18–2 3 microgram/ml depending on the amount given

The patients with toxaemia were classified according to the criteria of the American Committee on Maternal Welfare (Greenhill, 1955), mild and severe pre-eclampsia being differentiated

The following procedure was used for the extraction of vitamin B_6 from the blood

After withdrawal of blood by venepuncture it was allowed to clot (at 6°C) and serum was removed by centrifugation In a beaker 5 ml of serum, 5 ml of 1 per cent acetate buffer (pH 4 6) and 20 ml of distilled water were thoroughly mixed and the beaker immersed in boiling water (100°C) for 30 minutes After cooling the pH of the solution was adjusted to 6 5 with dilute sodium hydroxide and filtered through a glass sinter filter (Jena G IV) The volume was then made up to 10 times that of the blood used by adding the assay medium (Diding, 1955) The material was then assayed for vitamin B_6 activity using the method described by Diding (1955) with a pyridoxine auxotroph strain of E coli as test organism

Results

The results obtained in assays on the total series are shown in Table I

Table I *Serum Le el of Vitamin B6 Complex*

	Non pregnant Subjects					Normal Pregnancy	Pre-eclampsia
	Male	Female			Total Male and Female		
		Supposed Lndometrial Phase					
		Proli-ferative	Secre-tory	Men-strual			
Microgram vitamin B_6 per ml serum Mean ± standard deviation	0 037 ± 0 003	0 030 ± 0 035	0 010 ± 0 014	0 033 ± 0 011	0 014 ± 0 034	0 033 ± 0 034	0 0[illegible]5 ± 0 035
Number of estimations	5	9	6	3	23	26	10
Week of gestation						1[illegible]—40	16—40
Age in years	25—37	20—35	20—45	20—[illegible]		19—35	17—41

tablets, and this fact together with the declared high vitamin B_6 content of ordinary Swedish diet may explain the agreement between our results and those reported by Vilter

By the method we have used no difference in the levels of vitamin B_6 in blood from pregnant and non pregnant women can be demonstrated. In this respect our results confirm those of Friedman *et al* and Vilter *et al* Our results are also in agreement with the conclusions, outlined in the introduction, with the transaminase activity determinations as criteria, that there is no sign of a significant deficiency of vitamin B_6 in pregnancy Our results contrast with those of tryptophan loading tests, which suggest a real deficiency of vitamin B_6 The problem of specificity must, however, be raised in this respect. Whether the increased xanthurenic acid excretion is a physiological or a pathological variant in pregnancy is not known

It must be remembered that even though it is impossible to demonstrate a deficiency of B_6 in pregnancy there may be an increased *demand* for the vitamin The increased retention of ingested B_6 demonstrated by Wachstein and Gudaitis (1953 b) supports this idea Possibly the tryptophan load test is a sensitive indicator of such an increased demand

Our results do not suggest a deficiency of vitamin B_6 in toxæmia The series is too small to allow further evaluation but the results are in agreement with those of Wachstein and Gudaitis (1953 b)

Results from the loading tests show that vitamin B_6 rapidly appears in the blood after oral administration of pyridoxine

Summing up the evidence of a deficiency of vitamin B_6 in pregnancy is only circumstantial The high content of vitamin B_6 of ordinary Swedish diet and the commercial multivitamin tablets often given to pregnant patients seem sufficient to maintain the serum concentration of vitamin B_6 complex of pregnant women on the same level as that of non pregnant subjects It may, however be advisable to give higher doses of pyridoxine to pregnant women with excessive vomiting, toxæmia or unsatisfactory dietary intake

The amount of pyridoxine necessary when higher doses are indicated is difficult to state Wachstein and Gudaitis (1953

Discussion

Conclusions must be drawn from this study with some reserve because the blood samples were not collected under standardized conditions and the alimentary supply of vitamin B_6 was not strictly controlled

Half of our subjects presented values which were below the lowest detectable amount (0 030 microgram per ml) *In the calculation* of the means these values are put as zero

It is difficult to compare our values with the figures mentioned *in the* introduction (Marsh, Greenberg, and Rinehart, *1955*, Friedman *et al*, 1955, Vilter *et al*, 1954, Boxer *et al*, *1957*) No comparisons can be made with the determinations of Boxer *et* al because they determined the co-enzyme form of B_6 whereas we have determined total vitamin B_6 activity Also, our numerical values obtained in assays on pregnant women are not comparable with the results of other workers as none of the reports found in the literature of assays in pregnancy give numerical figures

Marsh *et al* used whole blood whereas Vilter *only mentions* 'blood' It is probable, however, that this means whole blood Serum was used in this study A very rough calculation of the B_6 content in whole blood of our subjects can be achieved in the following manner

Greenberg and Rinehart (1949) and Vilter (1956) report the B_6 compounds to be on the average equally distributed between plasma and the cellular elements of blood Thus two times our values would represent the values in whole blood of our subjects Applying such a correction, our values are in fairly good agreement with the average figure of 0 050 reported by Vilter but higher than those reported by Marsh *et al* The problem of the influence of the dietary intake of vitamin B_6 must, however, be raised in this respect Marsh *et al* give no information of the diet of their subjects but they report an increase to 0 085 microgram on the moderate intake of 15 mg pyridoxine per day Vilter estimates the average intake of his subjects to be 2 to 3 mg daily The majority of our pregnant subjects have consumed 6 mg pyridoxine per day administered as multivitamin

A daily supplement of about 10–15 mg pyridoxine in these complications is recommended

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b) and Zartman *et al* (1955) report 10 mg of pyridoxine daily to be adequate for preventing the abnormal excretion of xanthurenic acid in pregnancy Wachstein and Graffeo (1956) found a significantly lowered incidence of toxæmia in a group of 410 women receiving 10 mg pyridoxine per day as compared to controls A daily supplement of about 10–15 mg of pyridoxine in pregnancies complicated by vomiting, toxæmia or unsatisfactory dietary intake may be regarded as a reasonable measure

SUMMARY

Using a microbiological method of assay with a pyridoxine auxotroph strain of E coli as the test organism, determinations were made of the serum concentration of total vitamin B_6 complex in 23 healthy men and non-pregnant women with normal menses, in 26 women in the last trimester of an uncomplicated pregnancy, and in 10 women with toxæmia of pregnancy In 7 of the men and non-pregnant women pyridoxine loading tests were performed with subsequent determination of blood levels

No significant difference between the serum levels for the different groups of subjects could be obtained The mean ± standard deviation was for the men and non-pregnant women 0 034 microgram/ml serum ± 0 034, for the pregnant, healthy women 0 033 microgram/ml ± 0 034, and for the toxæmic women 0 025 microgram/ml ± 0 035 The loading tests showed that vitamin B_6 activity rapidly appears in the blood after oral administration of pyridoxine

The results are discussed and it is emphasized that conclusions from the figures must be drawn with some reserve since the alimentary supply of pyridoxine was not strictly controlled The high content of vitamin B_6 of ordinary Swedish diet and the commercial multivitamin tablets often given to pregnant patients seem sufficient to maintain the serum concentration of vitamin B_6 complex of pregnant subjects on the same level as that of non pregnant subjects It is only when the pregnancy is complicated with vomiting, toxæmia or unsatisfactory dietary intake that it seems indicated to supply the patients with higher doses of pyridoxine

xy estr-4 ene) has proved to have a good progestational effect animals without producing any side reactions The preparation *us has no* demonstrable androgenic effect and is a true, orally fective gestagen, since it can maintain pregnancy in spayed rats Madjerek *et al*, 1960) These experimental results have since een confirmed in clinical series (Borglin 1960 a) In that in-estigation allyl œstrenol was also tried in *a small series of* hreatened abortion

The most important indication for treatment with allyl œst-enol appears to be threatened or habitual abortion The earlier group of such cases (Borglin, 1960 a) has therefore since been extended and the results are given below

The Series and Methods

The series consisted of 104 cases In 97 of them treatment was given because of threatened or habitual abortion previous threatened abortion or premature delivery Prophylactically treatment was also given to women submitted to vaginal or abdominal operation during pregnancy In 7 of *the cases allyl œstrenol* was given to ascertain whether this substance could delay a legal abortion induced by intra amniotic injection of saline solution

In a previous paper (Borglin 1960 b) the effect of 17-α methyl 19 nortestosterone on threatened abortion was compared with that of injection of 17 α hydroxy progesterone caproate In the present investigation these two groups of patients were compared with patients treated with allyl œstrenol The group treated with 17 α methyl 19 nortestosterone was designated Group I that treated with 17 α hydroxy progesterone caproate, as Group II and that treated with allyl œstrenol, as Group III For comparison all three groups are included in the Tables

The patients treated with allyl œstrenol like those in the two previous series were selected at random Apart from the administration of allyl œstrenol treatment was the same as in the other two groups As in the previous investigations determinations were made of the activity of histaminase in the plasma, excretion of adreno-cortical steroids and pregnandiol in the urine, and vaginal smears were studied cytologically The results of

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ALLYL-ŒSTRENOL IN THE TREATMENT OF THREATENED ABORTION

BY

N E BORGLIN

Various treatments have been tried for threatened abortion, but as yet no ideal method has emerged One of the most important principles of treatment is, however, administration of corpus luteum hormone or substances with a similar effect Even when abortion is not due to insufficient production of progesterone, such therapy may be useful The possibility of administering large amounts of progesterone is limited by the fact that the hormone must be given parenterally and that it is relatively insoluble Local reactions, in the form of painful infiltration are common It is true that a derivative of progesterone, 17 *a* hydroxy progesterone caproate can be administered in large doses and with a relatively long effect, but its action is delayed

In recent years synthetic oral progestational substances have become available But most of them have only a weak effect or cause undesired side reactions The most effective progestational substances, derivatives of 19-nortestosterone often have a more or less marked androgenic effect with the risk of virilization of the mother or masculinization of the female fœtus

Recently de Winter *et al* (1959) prepared derivatives of 3-deoxo 19 nortestosterone and one of them, the allyl compound with the generic name of allyl œstrenol (17-α-allyl-17-β hyd

Allyl-œstrenol is the generic name of 17-α allyl 17 β hydroxy-estr 4-ene, the active principle of the preparation Gestanon (N V Organon Oss The Netherlands)

Table II *Indications for Treatment*

Indications		Group I	Group II	Group III
Threatened abortion		96	89	78
Habitual abortion	with threatened abort	10	4	6
	prophylaxis	3	3	6
		13	7	12
History of threatened abortion or premature delivery		3	—	3
Prophylaxis in association with operation	laparotomy	4	10	3
	vaginal surgery	5	4	1
		9	14	4
Other indications		5	7	—
Total		126	117	97

Allyl œstrenol was given by mouth in 5 mg tablets The daily dose varied between 5 mg and 30 mg In about half of the cases therapy was not started until a 24 hour sample of urine had been collected for hormone analysis and a blood sample had been drawn for determination of the plasma histaminase activity In the other cases treatment was started immediately on admission to hospital In cases of threatened abortion allyl œstrenol was continued until the threat had passed off or until it had become evident that abortion was inevitable In patients with habitual abor

Table III *Results of Treatment with Different Doses of Allyl-œstrenol*

Results	Allyl-œstrenol mg per day					Total
	5	10	15	20	30	
Missed abortion	2	1		2	2	7
Extra uterine pregnancy hydatidiform mole	1	2			1	4
Abortion during treatment (within 48 hours of admission to hospital)	1	8 (4)		1	8 (5)	18
Abortion after treatment and after the patient had left the hospital	1	4		1	3	9
Pregnancy went on to viability	4	18	4	8	25	59
Total	9	33	4	12	39	97

these examinations have been reported earlier (Borglin, 1960 a). In Table I the patients are divided according to age, previous pregnancies, and time of commencement of treatment before or after 20 weeks of pregnancy. The age distribution was about the same in all three groups, as was the ratio between the number of primigravidæ and multigravidæ. On the other hand, the number of cases treated after the 20th week of pregnancy was much smaller in Group III than in the other two groups. This might suggest that the tendency to abort was greater in this group, as it is widely accepted that the frequency of abortions is higher in the first months of pregnancy.

Table I. *Survey of the Series*

Age in Years	Group I[1]	Group II[2]	Group III[3]	(Therapeutic Abortion)
≤ 20	11	6	8	–
21 – 30	65	53	58	1
31 – 40	41	51	29	6
> 40	9	7	2	–
Total	126	117	97	7
Parity				
primigravidæ	32	33	35	–
multigravidæ	94	84	62	7
Treatment started				
≤ 20th week of pregnancy	99	90	89	7
> 20th week of pregnancy	27	27	8	–

[1] Group I: patients treated with 17-α methyl 19 nortestosterone.
[2] Group II: patients treated with 17-α hydroxy progesterone caproate or progesterone.
[3] Group III: patients treated with allyl-œstrenol.

The indications for treatment in the various groups are summarized in Table II. Prophylactic treatment because of different types of operation during pregnancy was given in only 4 cases in Group III as against 9 in Group I, and 14 in Group II. Apart from this the three groups are comparable.

on to viability and up to the present 30 infants have been delivered

The number of missed abortions was somewhat higher (7 out of 97) in Group III than in Group I (6 out of 126), and in Group II (5 out of 117) Group III included 2 cases of extra uterine pregnancy and 2 cases of hydatidiform mole Of the 30 children delivered, 27 weighed more than 2,500 g, and only in three cases was delivery premature This is a much lower frequency than in Groups I and II However, the series is too small to allow of any valid conclusions in this respect. Group III included no instances of malformation, no masculinization of the girls and no virilization or other side effects in the mothers

In four cases allyl-œstrenol was given prophylactically to women who were submitted to operation during pregnancy 1 vaginal operation (torsion of cervical polyp) and 3 laparotomies (2 cases of appendicectomy and 1 case of oophorectomy because of a large pseudomucinous cystadenoma) In all of these cases pregnancy went on to term without any sign of threatened abortion

There were 12 cases of habitual abortion and in 6 of these signs of threatened abortion were observed In 10 of these 12 cases pregnancy continued after treatment In only 1 of the cases did

Table V *Results of Treatment of Habitual Abortion*

Results	No of Cases	Abortion during Treatment	Pregnancy Continued				
			Total	Abortion Later	Premature	Full-term	Not yet delivered
Group I							
with threatened abortion	10	3	7	6	1	–	–
prophylaxis	3	1	2	–	1	1	–
Group II							
with threatened abortion	4	2	2	–	2	–	–
prophylaxis	3	–	3	–	–	3	–
Group III							
with threatened abortion	6	1	5	–	–	2	3
prophylaxis	6	1	5	1	–	3	1
Total	32	8	24	7	4	9	4

tion allyl œstrenol was given *for long periods, up to four months* On those days when the women would have been menstruating if they had not been pregnant (between 4th and 5th, 8th and 9th, 12th and 15th weeks of pregnancy, etc) the dose of allyl œstrenol was increased When used as a prophylactic in the treatment of patients submitted to operation during *pregnancy allyl* œstrenol was given from the day of admission until four to five days after operation Where possible operation was delayed until the treatment had been given for several days The daily doses used are listed in Table III

Results

The patients are grouped according to the results of treatment in the same way as in earlier studies The results of the pregnancies are given in Table IV In 59 of the 97 cases pregnancy went

Table IV *Results of Treatment and of Pregnancies*

Results	Group I	Group II	Group III
(1) Missed abortion	6	5	7
(2) Extra-uterine pregnancy, hydatidiform mole	1	1	4
(3) Abortion during treatment	37	35	18
a) within 48 hours of admission to hospital	14	8	9
(4) *Abortion after the treatment and* after the patient had left the hospital	19	7	9
(5) Pregnancy went on to viability	63	69	59
Of Group 5			
a) delivered at term (birth weight > 2 500 g) — boys	28 } 52	30 } 58	7 } -7
— girls	-4	28	20
— died	—	1	—
b) delivered before term (birth weight ≤ - 500 g) — boys	5 } 11	5 } 11	3 } 3
— girls	6	6	—
— died	4	4	2
Twins — term	—	1	—
Twins — premature	—	1	1
Serious malformations — abortions	1	—	—
Serious malformations — viable fœtuses	3	—	—

24 hours in 2, and within 48 hours in the remaining 5 Allyl-œstrenol had been given until abortion had occurred These results do not *differ appreciably from* those obtained in an untreated series, but the effect of allyl œstrenol in such cases is receiving further attention

Discussion

Judging from animal experiments allyl œstrenol has no androgenic or œstrogenic properties and no inhibitory effect on the gonads or adrenal cortex Neither does it appear to have any toxic or other undesired side effects (Madjerek *et al*, 1960) This steroid possesses the unusual property of being able to maintain pregnancy in spayed pregnant rats when administered orally This together with the absence of untoward effects of the substance naturally has led to the assumption that it might be an almost ideal substance for the treatment of threatened abortion in human beings The results obtained in a preliminary investigation in 43 cases were also promising (Borglin, 1960 a), as well as in 30 cases in the series of another investigator (Willemsen, 1960)

The results obtained in experimental animals have been confirmed Allyl œstrenol was found to produce no side effects, at least not in this relatively small series In that investigation (Borglin, 1960 a) it was also shown that allyl œstrenol is not excreted as pregnandiol and that it does not seem to influence the plasma histaminase activity, which is of importance in assessing the prognosis for the pregnancy (Borglin and Willert 1957) Cytological examination of vaginal smears showed that the pattern had become normal in most cases during treatment with allyl œstrenol and no signs of an androgenic effect could be demonstrated

In the present investigation, which is based on a larger series, the number of pregnancies that continued was larger or at least as large as that in the series treated with 17 α methyl 19-nortestosterone by mouth or 17 α hydroxy progesterone caproate parenterally Allyl œstrenol appeared to have a particularly good effect on habitual abortion

abortion occur after cessation of the treatment (Table V) Of the remaining 9 women, 4 are still undelivered, but 5 were delivered at term (i e a larger number than in Groups I and II together) If the premature deliveries are also included in Groups I and II the total number of successes in these groups is 8 out of 20, while the number in Group III is 9 out of 12, a definitely better result.

The results of treatment are summarized in Table VI

Table VI *Results of Treatment*

	Viable Foetuses in Total Series	No of Pregnancies which Continued after Treatment[1]	No of Viable Foetuses[2]
Group I	50 0 % (63 out of 126)	73 9 % (82 out of 111)	68 5 % (63 out of 92)
Group II	59 0 % (69 out of 117)	70 4 % (76 out of 108)	68 3 % (69 out of 101)
Group III	60 8 % (59 out of 97)	81 0 % (68 out of 84)	78 7 % (59 out of 75)

[1] This calculation refers to the entire series, Groups 2 and 3 a in Table IV being excluded

[2] This refers to the entire series, Groups 2, 3 a, and 4 in Table IV (see text) being excluded

As in the previous Tables the results obtained in Group III are compared with those noted in Groups I and II and all three groups are judged according to the same principles Whatever criteria are used in the evaluation of the results, those achieved in patients treated with allyl œstrenol are better than in the patients in the other two groups

In 7 cases of therapeutic abortion allyl œstrenol was given in a dose of 30 mg a day for three to seven days before intra amniotic injection of saline solution After such an injection (100 ml -150 ml of amniotic fluid is removed by a cannula introduced through the abdominal wall and replaced by a corresponding amount of 20 per cent NaCl) abortion usually occurs within 48 hours Of these 7 cases treated with allyl œstrenol, abortion occurred within

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MARFAN'S SYNDROME AND PREGNANCY

BY

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Marfan s syndrome is an uncommon but not rare, inherited, selective disorder of the connective tissue The skeleton eyes, and the cardio-vascular system are most often affected The cause of the condition is unknown The syndrome was first described by Marfan (1896) as *dolichostenomelia* Since the fingers are long and spidery in patients with this disorder Achard (1902) called it *arachnodactyly* The heredity of the syndrome and its supposed mesodermal origin are indicated by the name suggested by Weve (1931) *i e dystrophia mesodermalis congenita typus Marfanis* Reviews of the syndrome have recently been published by McKusick (1960) Asperger and Cecchini (1960) and Sinclair *et al* (1960)

Of the cardio-vascular lesions dissecting aneurysms in the aorta and the large vessels (Baer *et al* 1943, Etter and Glover 1943) are common and the risk of rupture is a life threatening danger to these patients which is believed to be augmented by pregnancy (McKusick 1960) and several cases of aortic rupture in association with pregnancy have been reported (Lindeboom and Bouwer 1950 Spenser 1952 Husebye *et al* 1958 Novell *et al* 1958)

A case of Marfan s syndrome recently seen by us is now described

The present study does not permit any conclusions as to the optimal dose of allyl-œstrenol A dose of 30 mg a day did not appear to produce better results than 10–20 mg a day This point requires investigation on a larger series

SUMMARY

A series of cases of threatened abortion, habitual abortion, and cases operated upon during pregnancy were treated with allyl œstrenol by mouth The results of this treatment were compared with those obtained in similar groups of patients treated with 17-α-methyl-19-nortestosterone or with 17-α hydroxy progesterone caproate The investigation showed

(1) that allyl-œstrenol has a pregnancy-maintaining effect that is stronger or just as strong as that of the other two substances considered,

(2) that allyl-œstrenol has no side effects such as virilizing effects on the mother or masculinizating influence on a female fœtus

It thus seems that allyl œstrenol is one of the best preparations available for the treatment of threatened or habitual abortion

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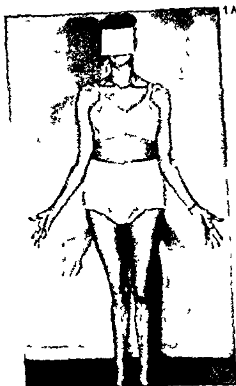






Fig 1 A, antero-posterior view, B Lateral view Note the long limbs with poor musculature, genu recurvatum kyphosis cubitus valgus clinodactyly of fifth finger on right hand A pulsating tumour possibly an aneurysm, in the common carotid artery is seen in the neck. (C) The feet, toes, hands and fingers are long and spidery The pelvis is broad.

Report of Case

The patient was a 23 year-old, married woman (Record No 2764/60), who had always been tall and slender At 9 years her height was 149 cm and she weighed 30 kg, she was now 183 cm and weighed about 60 kg Her father was said to have been tall and slender but, otherwise the family history was negative

At 3 years she was found to have heart disease, for which she was subsequently in hospital several times A harsh systolic murmur could be heard, maximal at the apex Repeated electrocardiography revealed no abnormalities During pregnancy, however, coupled ventricular extrasystoles had been noted X ray examination had shown a normal sized heart with a rounding of the left ventricle and the finding had been interpreted as an aortic valvular disease or a septal defect No firm diagnosis was made The supposed organic heart disease had never produced any evidence of cardiac decompensation or other symptoms

At 12 years she had suffered from meningitis, but had otherwise always felt well She had never had any gynæcological complaints and had never before been pregnant Wasserman s reaction was negative

The last menstruation was on 21st Feb 1960, she noticed fœtal movements for the first time in the beginning of July, and delivery was expected on 28th Nov 1960 Obstetrical examination at various stages of pregnancy revealed no signs of any pathological condition However, the strange appearance of the patient (Fig 1), the long slender limbs, the spidery fingers and toes (Fig 2), pectus excavatum and other unusual features suggested the possibility of Marfan s syndrome and the patient was admitted for observation Closer investigation gave the following findings

Skeleton The patient had not only long slender limbs, fingers and toes, a disproportionately long first toe but also genu recurvatum, cubitus valgus, clawing of the fifth finger of the right hand (clinodactyly), a broad pelvis (Table I), kyphosis poor musculature and scanty body fat, all of which contributed to the picture of dolichostenomelia

X ray examination of the hands and feet (Fig 3) showed long, spidery fingers and toes The longest finger was more than 1 5 times the length of its metacarpal

Cardio-vascular system In addition to the features mentioned above, there was a pulsating vascular tumour or aneurysm of the common carotid artery on the left side (See Fig 1 C) The volume of the heart was 700 ml, which corresponds to 390 ml per m^2 body surface The aorta was not increased in width or length Chest X-ray showed nothing of note (Fig 4) The blood pressure was normal through pregnancy

Eyes Ophthalmological examination revealed myopia but no other abnormalities, thus no ceratoconus, no megalocornea or dislocation of the lenses and no iridodonesis

Since the risk of complications is said to be greatest during the last weeks



Fig 3 Radiographs of hands and feet showing the long phalanges The longest finger is more than 1 5 times the length of the metacarpal





Fig 2 Patient s hands and feet showing the long spidery fingers and toes Note the disproportionately long first toes



Fig 5 The baby – which shows no definite signs of Marfan's syndrome though the great toes are rather long

of pregnancy and during spontaneous labour the woman was delivered by Cæsarean section in the 37th week of pregnancy The post-operative course was uneventful The child a girl weighed 3,050 g and was 49 cm. long The child showed no characteristics of Marfan's syndrome except that the great toes were possibly somewhat long (Fig 5)

About two months after delivery and for no apparent reason the patient suddenly became ill with signs of cardiac failure Pulmonary œdema developed and 3 days later the patient died Autopsy showed an incomplete aortic rupture with a dissecting aneurysm typical of Marfan's syndrome The lesion extended from close to the heart to a few centimetres along the common iliac artery on either side The pulsating tumour observed on the left side of the neck proved to be due to venectasiæ in the region of the carotid artery



Fig 4 Chest X ray showing no specific abnormality

Table I *Various Measurements of Patient*

Arm span	187 cm
Body height	183 cm
vertex – symphysis pubis	92 cm
symphysis to floor	91 cm
Pelvic measurements	
inter spinous diameter	33 cm
inter cristal diameter	35 cm
external conjugate	21 cm
Length of the first toe	8 5 cm

Length of fingers

	Right	Left
Dig I	8 2 cm	7 9 cm
II	11 8 cm	11 9 cm
III	12 7 cm	13 2 cm
IV	12 4 cm	12 3 cm
V	9 4 cm	9 3 cm

Metacarpal index (according to Sinclair *et al* 1960), 8 3

ting aneurysm and aortic rupture (Nodes and Hinds, 1900, Sheehan, 1939, Schnitker and Bayer, 1944, Mandel, Evans and Walford, 1954, Hirst, Johns, and Kime, 1958) probably because of the increased strain of pregnancy and labour It is possible that some endocrine factors may also contribute to increase the risk of complications

Only 3 cases of aortic aneurysm in association with pregnancy or the puerperium have been diagnosed as Marfan s syndrome before autopsy (Lindeboom and Bouwer, 1950, Carpent et al 1956 Husebye et al, 1958) In most cases the diagnosis was not made until after death An early diagnosis is probably of great prognostic importance in the event of pregnancy These patients at least those with severe vascular lesions, should try to avoid pregnancy and should pregnancy occur, legal abortion, possibly with sterilization should be considered

In our case no serious cardio-vascular changes could be demonstrated with certainty before the final acute illness Legal abortion was offered but the patient refused For obvious reasons it is difficult for patients with Marfan s syndrome to realize the seriousness of their condition Once a dissecting aneurysm has developed all treatment is futile

SUMMARY

A case of Marfan s syndrome in association with pregnancy is described The diagnosis ætiology, frequency and therapeutic possibilities are discussed The increased risks of complications during pregnancy and labour are stressed The syndrome though uncommon is probably not rare, and it is one of the causes of sudden death in association with pregnancy

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Discussion

The patient had several of the features characteristic of Marfan's syndrome The skeleton was disproportional with dolichostenomelia, arachnodactyly, clinodactyly, kyphosis, and loose joint capsules with consequent genu recurvatum and cubitus valgus She was myopic and had some intra cardiac abnormality and, possibly even before pregnancy, a lesion of the ascending aorta Data available suggest that her father may have had the same condition The presence of ectopia lentis is no longer regarded as necessary for a diagnosis of Marfan's syndrome The changes mentioned above, noticed on examination at the Prenatal Clinic, were sufficient for an unequivocal diagnosis of Marfan's syndrome The management of such a case is, however, debatable

Marfan's syndrome is probably more common than might be imagined from perusal of the literature (McKusick, 1960) It is widely believed that many mild cases of the disease (*forme fruste*) occur (McKusick, 1960) About 400 cases have been published It appears that the condition occurs in all races and that the sexes are equally affected It is dominant in inheritance

The cause of the changes in Marfan s syndrome is unknown Most authors believe it to be a metabolic disorder of the connective tissue, to be precise, of the elastic fibres The most conspicuous feature, dolichostenomelia, may be ascribed to defective periosteum An increased excretion of hydroxy-proline (Sjoerdsma *et al*, 1958) suggests that the metabolic disorder of the collagen tissue may be the primary cause of the condition Bacchus (1958, 1960) found the serum mucoprotein level to be low in a family with Marfan s syndrome, but McKusick (1960) was unable to confirm this finding in his patients Changes (kyphosis, kyphoscoliosis, hernia, aortic aneurysm) similary to those seen in Marfan s syndrome can be produced in rats by feeding them seeds from *Lathyrus odoratus* (Ponseti *et al* 1952, 1954)

Since the ætiology of Marfan s syndrome is unknown, no specific therapy is available Some of the symptoms can be relieved by surgery and orthopædic treatment Judging from the scant literature on the subject, pregnancy increases the risk of dissec

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FŒTAL UPTAKE OF PHOSPHATE IN PROLONGED GESTATION IN RABBITS

BY

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In clinical obstetrics it is a well established fact that the incidence of intra uterine fœtal death increases if pregnancy is prolonged In the rabbit in which gestation can be artificially prolonged with progesterone (or gonadotrophin) the same can be observed The increase in the fœtal death rate starts within twenty four hours after term, and four days after term all the fœtuses are found dead (Csapo 1955 Fuchs and Fuchs, 1958) The progesterone given to the maternal rabbit is not likely to be the direct cause of death, since it can be given in considerably larger doses before term without any effect upon the viability of the fœtuses Nor is difficult delivery of the oversized fœtuses responsible for the fœtal loss since the fœtuses are found dead in the uterus before labour begins

The increased fœtal mortality in prolonged gestation has been ascribed to placental insufficiency Oxygen is generally considered the most vital of the substances to be supplied to the fœtus but it is not known whether oxygen insufficiency is the sole deprivation suffered by the fœtus

It was decided to investigate the transfer of phosphate to the rabbit fœtus in prolonged gestation because of the important role of phosphorus in cellular metabolism From earlier work on the placental transfer of phosphate in the guinea pig it was known that the saftey margin of the supply of phosphorus becomes very

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FŒTAL UPTAKE OF PHOSPHATE IN PROLONGED GESTATION IN RABBITS

BY

ANNA RIITTA FUCHS AND FRITZ FUCHS

In clinical obstetrics it is a well established fact that the incidence of intra uterine fœtal death increases if pregnancy is prolonged In the rabbit in which gestation can be artificially prolonged with progesterone (or gonadotrophin), the same can be observed The increase in the fœtal death rate starts within twenty four hours after term, and four days after term all the fœtuses are found dead (Csapo 1955, Fuchs and Fuchs, 1958) The progesterone given to the maternal rabbit is not likely to be the direct cause of death, since it can be given in considerably larger doses before term without any effect upon the viability of the fœtuses Nor is difficult delivery of the oversized fœtuses responsible for the fœtal loss, since the fœtuses are found dead in the uterus before labour begins

The increased fœtal mortality in prolonged gestation has been ascribed to placental insufficiency Oxygen is generally considered the most vital of the substances to be supplied to the fœtus but it is not known whether oxygen insufficiency is the sole deprivation suffered by the fœtus

It was decided to investigate the transfer of phosphate to the rabbit fœtus in prolonged gestation because of the important role of phosphorus in cellular metabolism From earlier work on the placental transfer of phosphate in the guinea pig it was known that the saftey margin of the supply of phosphorus becomes very

narrow toward the end of gestation (Fuchs and Fuchs, 1957, Fuchs, 1957) The rabbit was considered more convenient for studies of prolonged gestation than the guinea pig, because its gestation period is much shorter and because it is easy to determine the time of conception accurately

Methods

Virginal Danish White Land Rabbits of uniform breed and of approximately the same age and weight were mated under supervision In previous studies the average length of gestation in this breed was found to be 31 days

One group of rabbits were given 5 mg progesterone in oil intramuscularly from a gestation age of 29 days and daily until the operation one to six days later Another group of rabbits, to be studied before term, was not given progesterone

The transfer of phosphate to the fœtuses was studied with the aid of radioactive phosphorus which was injected as orthophosphate into an ear vein of the mother animal Abdominal hysterotomy was performed, generally thirty minutes later, and the fœtuses and the placentæ were removed Care was taken to avoid blood loss from the umbilical vessels and the placenta Usually four fœtuses and four placentæ were ashed individually for total phosphorus and radiophosphorus determinations When the litter contained more than four fœtuses, an attempt was made to collect blood from the umbilical vein of the remaining fœtuses During the experiment a number of blood samples were withdrawn from the carotid artery of the mother to determine the rate of disappearance of radiophosphate from the plasma The concentration of inorganic phosphate was determined in the maternal plasma in each experiment, and in the fœtal plasma when this was available

The amount of phosphate transferred to the fœtus during the experiment was calculated from the amount of radiophosphorus found in the fœtus at the end of the experiment and the average specific activity in the maternal plasma during the period, as previously described (Fuchs and Fuchs, 1957, Fuchs 1957)

Results

The litter size varied between 3 and 10 fœtuses Of the litters studied before or at term, two contained one dead fœtus each In the progesterone-treated group 2 fœtuses out of 10 were found dead in a litter removed 33 days after mating, while all fœtuses removed earlier were alive At 34 days 2 hours a whole litter of 6 was alive, whereas litters removed at 34 days 18 hours and at 35 days, with 3 5, and 9 fœtuses, were all dead

The concentration of inorganic phosphate in the maternal plasma varied widely No relation could be found between the plasma phosphate concentration and the period of gestation, except in prolonged pregnancies where the concentration showed a sharp rise after the 32nd day When fœtal plasma was examined, it always had a higher concentration of inorganic phosphate than the maternal plasma The same has been found in the human, in the guinea pig and in other species

The total phosphorus content of the rabbit fœtus (Fig 1) increases at a faster rate than the body weight in the last half of gestation During this period neither the weight nor the phosphorus content of the placenta varies significantly Even after term both the fœtal weigth and the phosphorus content increase, but the phosphorus concentration in the fœtus ceases to rise, as can be seen from Fig 2 This finding is significant, because while weight and total phosphorus vary considerably from the 27th day, the fœtal phosphorus concentration is fairly constant within a litter and from litter to litter It is independent of litter size and depends only upon gestation age The placental phosphorus concentration varies but little with gestation age though there is a definite increase when the fœtuses are dead

Fig 3 shows the fœtal uptake of phosphate per 24 hours calculated from the uptake of radiophosphate during the experiments If it is compared with the total phosphorus retention per 24 hours calculated from Fig 1 the phosphate uptake does not cover the total phosphorus need The need is covered only if the amount of phosphate which during the experiments is taken up by the placenta is added. In some cases of late gestation even the combined uptake fails to cover the fœtal needs but this is probably due to

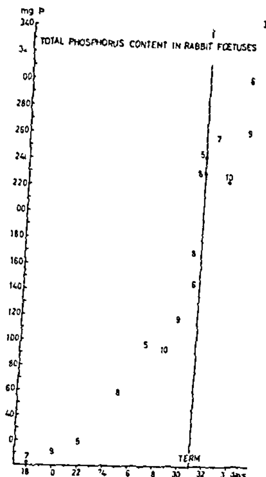


Fig 1 Average total phosphorus content per fœtus in the second half of gestation and in prolonged pregnancies in the rabbit The filled circles indicate progesterone treated, the open circles non treated rabbits The numbers indicate litter size

certain sources of error of the experimental method which are discussed in detail elsewhere (Fuchs and Fuchs, 1961) At any rate, there is no safety margin in later pregnancy In the guinea pig the safety factor, i e, the ratio between the transferred and retained amounts, was found to be less than 1 5 at the end of gestation (Fuchs and Fuchs, 1957, Fuchs, 1957) If phosphorus is not transferred to the fœtuses in other forms than the inorganic phosphorus measured in present experiments, and there is no

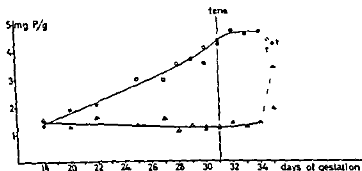


Fig 2 Fœtal and placental phosphorus concentration in the second half of gestation and in prolonged pregnancies.

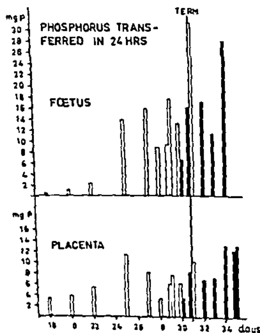


Fig 3 Fœtal and placental uptake of phosphate per 24 hours, calculated from the uptake of radiophosphate in 30 minutes. Black columns indicate progesterone-treated rabbits.

evidence for such transfer, it is possible that the fœtuses do not always get enough phosphorus at the end of gestation

After term the phosphorus uptake does not increase further but remains on about the same level until the fœtuses die. This would seem to indicate that either the placenta is unable to increase the transfer, or the mother is unable to mobilize enough phosphate to increase the fœtal phosphorus concentration. As the maternal plasma phosphate appears to rise after term, it must be the placenta which has reached the limit of its capacity

In the 3 cases with dead litters around day 35 fœtal death appeared to have occurred a considerable period of time before in 1 case, and the partly separated placentæ were not examined. In the 2 other cases the placentæ appeared to be intact, and the rate of uptake in the placentæ was as high as about 13 mg in 24 hours, while no more radiophosphate could be found in the fœtuses than could be explained by contamination with maternal blood at operation. Since even the placental phosphorus concentration was increased, it is evident that the placentæ must have been alive after fœtal death and continued to accumulate phosphorus. The placental uptake of radiophosphate in these 2 cases is as high as on any previous day, but not as high as the combined fœtal and placental uptake, had the fœtuses been alive

Discussion

These experiments show, as did our previous experiments in guinea pigs, that inorganic phosphate is transferred from the maternal to the fœtal blood against a concentration gradient. This requires an active transport mechanism which must be localized to the chorionic cells, probably at their boundary toward the intervillous space. In the placenta a pool of phosphorus is formed from which the fœtus is supplied

During fœtal development phosphorus is incorporated in larger amounts than any other mineral except calcium. The total phosphorus concentration increases until term, but in prolonged gestation there is no further increase. Inorganic phosphate is transferred from the maternal plasma in sufficient amounts to account for

the fœtal phosphorus deposition in most cases At the end of gestation the fœtuses may not always get enough phosphorus and consequently develop at less than the optimal rate

In 1956, Klein published similar experiments in rats His results indicate a rapid fall in placental permeability after term However, his technique (prolongation of pregnancy by supra vaginal ligature of the uterine horns) and his methods of calculation (neglecting the concentration of inorganic phosphate in the maternal plasma and the placental uptake of radiophosphorus) is open to severe criticism The results of the present experiments do indicate a relative reduction of placental function after term, but there is no sharp fall It is impossible to say whether this relative insufficiency with regard to the transfer of phosphate can be a contributing cause of intra uterine fœtal death

It is interesting to note that the placentæ stay alive for some time after fœtal death and continue to accumulate phosphate This indicates that the removal of phosphate from the maternal blood by the placenta is independent of the fœtus The same has been shown for iron by Bothwell et al (1958) and for zinc by Terry et al (1960)

SUMMARY

The transfer of phosphate from mother to fœtus in prolonged gestation was studied in rabbits with the aid of radioactive phosphorus Pregnancy was prolonged with daily injections of 5 mg progesterone The previous observations of increased fœtal mortality after term was confirmed The fœtal phosphorus concentration which increases during normal gestation, does not increase further after term indicating a relative placental insufficiency with regard to phosphorus After intra uterine fœtal death however the placentæ remain alive at least for some time and continue to accumulate phosphorus

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STAPHYLOCOCCAL DISSEMINATION AND SEPSIS IN INFANTS

BY

P. HELMS AND A. STENDERUP

The purpose of the present study was (i) to clarify the incidence of endemic pyogenic infections in infants, (ii) the relationship of these infections to the place of birth (i. e. hospital versus home) and to nasal colonisation with Staphylococcus aureus and (iii) the significance of this micro-organism in superficial pyogenic infections occurring during the first two months of life. The investigations were performed on infants born in the State Maternity Hospital for Jutland and infants born at home in the city and county of Aarhus (population 215 900) during the last nine months of 1959.

This study was preceded by a review of the records made out by the health visitors for infants born in the city and county of Aarhus in 1956 and 1957 (**Helms** and **Stenderup**, 1961). These records contained detailed information of the clinical infections in which we were interested and revealed that infections had occurred in 920 infants under two months of age out of a total of 6 383 or 14.4 per cent (15.4 per cent of infants born in the Maternity Hospital and 13.5 per cent of those born at home). The two most frequent diagnoses were purulent conjunctivitis (5.5 per cent) and skin infections (8.0 per cent). Fig. 1 shows the 920 cases distributed according to the week of life in which the in-

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During November and December 1959, nasal swabs were obtained both on the seventh day of life and at the age of one month in all infants born at home

The investigations performed in the State Maternity Hospital for Jutland comprised (i) nasal swabs from all infants on the seventh day of life, (ii) nasal swabs from their mothers taken at the same time, and (iii) swabs from all infections observed The medical and nursing staffs were studied by nasal swabs every third month and so were new members on their appointment Apart from cases of manifest infection the swabs were always taken by one of us (P H)

After discharge from the hospital the infants were swabbed in the nose by the Health Visitors at the age of about one month

The State Maternity Hospital for Jutland serves the population of the entire peninsula is the teaching hospital of the University of Aarhus and trains nurses Accordingly, there are many changes both in the nursing staff and in the medical students working in the hospital Both normal and abnormal births occur and about one half of the patients originate from the district covered by the present study The hospital has about 2,000 births every year, it has 55 beds distributed in wards with from one to six beds

Healthy infants are kept and nursed in the room occupied by their mothers while diseased and premature infants are placed in a special isolation ward with 12 bassinets and four incubators In this ward the nurses wear special uniforms and face masks, but otherwise no special measures are taken apart from the application of strict aseptic precautions

A sterile dressing is applied to the umbilicus immediately after the delivery this dressing is changed every day under sterile precautions but without the use of antiseptics

Healthy infants are kept in hospital for eight or nine days according to the distance to their homes

Bacteriological studies

Ordinary cotton wool swabs were used from which the material obtained was transferred directly to blood agar for culture Coagulase-positive hæmolysing colonies were isolated From a single

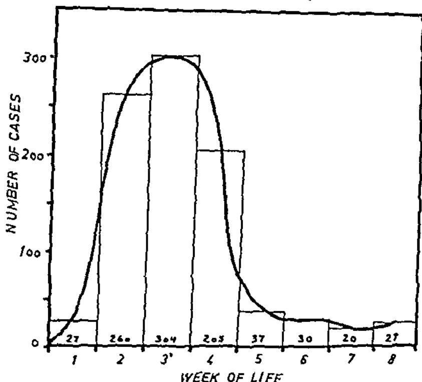


Fig 1 Distribution according to the time of onset in 920 cases of superficial clinical infections observed during the first eight weeks of life in infants born in the city and county of Aarhus in 1956 and 1957

fections started Of the infections about 87 per cent began within the first month of life, while such infections were rarely observed after the end of the second month

Present Investigation

On the basis of these data we determined to concentrate on studies of the infants during the first four weeks of life In 1959, collaboration with the health visitors commenced They agreed (i) to obtain nasal swabs from all infants born at home when they were about one month old, (ii) to submit information of all observed or reported clinical infections during the first two months of life, and (iii) to take swabs from these infections if they were still present at the visit The nasal swabs taken at the age of one month were sent to our laboratory accompanied by a printed form on which it was expressly stated if no infections had occurred

sation rate was slightly higher in male than in female infants Nasal swabs secured on the seventh day of life showed the same rates in infants born in the Maternity Hospital and in those born at home At the age of one month, the nasal carrier rate was a little higher (53 per cent) in infants born in the Maternity Hospital than in those born at home (41 per cent)

Analysis of the Phage Type and Penicillin Resistance of the Isolated Strains

During the period of investigation (1st March to 31st Dec, 1959), no outbreaks of staphylococcal infections occurred among the staff or the patients of the Maternity Hospital, and phage typing did not reveal any particular type or type pattern which could be regarded as a typical hospital strain An attempt was therefore made by studying larger groups to define standards of characteristic hospital strains and of 'home strains

As representatives of carriers of hospital strains we chose the nurses of the Maternity Hospital As most of the student nurses were examined only once while the members of the permanent nursing staff were examined repeatedly, this analysis was based on the number of strains of staphylococci isolated by nasal swabs from nurses instead of on the number of individuals studied In all surveys of the members of the nursing staff the nasal carrier rate was about 40 per cent with only very slight fluctuations from time to time

Table II shows a comparison of staphylococcal strains isolated from the nursing staff and from groups of individuals without direct hospital contacts i e infants born at home and mothers on admission to the Maternity Hospital (Only a minority of the mothers were examined both on admission and seven days after delivery)

The two groups presented two characteristic differences (i) the percentage of penicillin resistance was much higher in hospital strains than in home strains (89 as against 41 per cent) (ii) the percentage of hospital strains belonging to Phage Group I was higher than in home strains (35 as against 20 per cent) Type 80 plus type 52/52A/80 occurred in 16 and 6 per cent respectively

Table III shows the results of nasal swabs from infants and

colony, the sensitivity to penicillin, streptomycin, chloramphenicol, and terramycin was determined by means of sensitivity tablets from the Roskilde Medical Company, the sensitivity was expressed by the diameter of the zone of inhibition in millimetres All coagulase-positive strains were submitted to phage typing (Rosendal, 1959) at the State Serum Institute, Copenhagen, while all other studies were performed in the Institute of General Pathology, Aarhus

The individual strains were characterised by their phage type and sensitivity to penicillin Strains with the same phage pattern and the same sensitivity to penicillin were taken to be identical, while those with significant differences in the sensitivity to penicillin or with more than one deviation in the phage pattern were considered to be different

Strains with a sensitivity to penicillin of 26 mm or more were characterised as penicillin sensitive, while those with a zone of inhibition of 25 mm or less were put down as penicillin resistant

Frequency of Nasal Carriage of Staph Aureus in the Infants Studied

Table I *Survey of the Carrier rate of Staph Aureus Revealed by Nasal Swabs Obtained on the Seventh Day of Life and at the Age of One Month in 2 748 Infants Born in the Maternity Hospital or at Home*

Place of Birth	Sex	Nasal Swabs on Seventh Day			Nasal Swabs at One Month		
		No of Cases	Staph. Aureus Present		No of Cases	Staph. Aureus Present	
			No	%		No.	
Maternity hospital	Male	842	362	43	468	256	57
	Female	735	261	36	410	191	47
	Total	1,577	623	40	878	447	53
At home	Male	147	71	46	714	304	43
	Female	112	46	41	698	278	40
	Total	259	117	45	1 412	582	41

Table I shows the results obtained by nasal swabs from 2 748 infants, of whom 1,126 were studied twice, viz on the seventh day of life and at the age of one month In all groups the coloni

Analysis of the Sources of Infection of Infants in the Maternity Hospital Based on Nasal Swabs

The analysis of phage types and penicillin resistance of staphylococci isolated by nasal swabs from infants born in the Maternity Hospital suggests that the infants had been infected by hospital strains and not by those carried by the mothers A closer analysis of the relation between strains isolated from mothers and from infants appears from Tables IV and V

Table IV *Correlation Between the Results of Nasal Swabs in the Infants and Their Mothers*

Infants	Mothers	No.	%
A Staph aureus absent	Staph. aureus absent	673	46
B Staph aureus absent	Staph. aureus present	195	13
C Staph aureus present	Staph. aureus absent	313	22
D Staph aureus present different from mother's	Staph aureus present	142	10
E Staph aureus present identical with mother's	Staph aureus present	127	9
Total		1 450	100%

Table IV shows that 13 per cent of the infants were negative (without Staph aureus) although their mothers were positive (with Staph aureus) 22 per cent of the infants were positive with negative mothers In 10 per cent of the infants, the strains differed from those isolated in the mothers, and only in 9 per cent did infants and mothers reveal the same strain in the nose

Table V *Resistance and Phage-type Analysis of the Strains of Staph Aureus Isolated in the Infants and Their Mothers*

	C	D		E
	Infant	Infant	Mother	Infant + Mother
No of strains	313	142	142	127
Penicillin resistant %	82	79	42	56
Phage-group I %	34	30	23	27

Table V shows the resistance/phage analysis of the last three groups in Table IV Group C are children with negative mothers

Table II *Comparison Between 'Hospital Strains, i e Staph Aureus Isolated from Nurses in the Maternity Hospital, and Home Strains, i e Staph Aureus Isolated from the Group without Direct Hospital Contacts*

Nasal Swabs in 1959	Hospital Strains (Nurses)	Home Strains		
		Infants Born at Home		Mothers on Admission to Maternity Hospital
		On 7th Day	At 1 Month	
No of swabs	702	259	1,412	206
Staph aureus present number	287	117	582	45
Staph aureus present %	41	45	41	22
Penicillin resistant, %	89	32	43	33
Types 80 + 52/52A/80, %	16	7	6	6
Phage-group I, total, %	35	16	20	17
Phage-group II, %	19	30	29	30
Phage group III, %	21	16	22	22
Non typable, %	16	22	10	22

Table III *Nasal Swabs from Infants and Mothers Obtained on the Seventh Day after Delivery in the Maternity Hospital in 1959*

	Infants	Mothers
No of swabs	1,577	1,582
Staph aureus present number	623	504
Staph aureus present %	40	32
Penicillin resistant, %	77	45
Types 80 + 52/52A/80	12	8
Phage group I total, %	32	23
Phage group II, %	28	31
Phage group III, %	21	16
Non typable, %	9	19

mothers seven days after delivery On the basis of the above mentioned criteria, a distinct difference was revealed in the staphylococcal strains, harboured by infants and mothers Hospital strains were predominant among the infants and home strains predominated among the mothers

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Nasal Swabs in 1959	Hospital Strains (Nurses)	Home Strains: Infants Born at Home, On 7th Day	Home Strains: Infants Born at Home, At 1 Month	Home Strains: Mothers on Admission to Maternity Hospital
No of swabs	702	259	1,412	206
Staph aureus present number	287	117	582	45
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Phage-group I, total, %	35	16	20	17
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Phage group III, %	21	16	22	22
Non typable, %	16	22	10	22

Table III *Nasal Swabs from Infants and Mothers Obtained on the Seventh Day after Delivery in the Maternity Hospital in 1959*

	Infants	Mothers
No of swabs	1,577	1,582
Staph aureus present number	623	504
Staph aureus present %	40	32
Penicillin resistant, %	77	45
Types 80 + 52/52A/80	12	8
Phage-group I, total, %	32	23
Phage-group II %	28	31
Phage-group III, %	21	16
Non typable, %	9	19

mothers seven days after delivery On the basis of the above-mentioned criteria, a distinct difference was revealed in the staphylococcal strains, harboured by infants and mothers Hospital strains were predominant among the infants and home strains predominated among the mothers

Analysis of the Sources of Infection of Infants in the Maternity Hospital Based on Nasal Swabs

The analysis of phage types and penicillin resistance of staphylococci isolated by nasal swabs from infants born in the Maternity Hospital suggests that the infants had been infected by hospital strains and not by those carried by the mothers. A closer analysis of the relation between strains isolated from mothers and from infants appears from Tables IV and V.

Table IV *Correlation Between the Results of Nasal Swabs in the Infants and Their Mothers*

Infants	Mothers	No.	%
A Staph. aureus absent	Staph. aureus absent	673	46
B Staph. aureus absent	Staph. aureus present	195	13
C Staph. aureus present	Staph. aureus absent	313	22
D Staph. aureus present, different from mother's	Staph. aureus present	142	10
E Staph. aureus present, identical with mother's	Staph. aureus present	127	9
Total		1 450	100%

Table IV shows that 13 per cent of the infants were negative (without Staph. aureus) although their mothers were positive (with Staph. aureus). 22 per cent of the infants were positive with negative mothers. In 10 per cent of the infants, the strains differed from those isolated in the mothers, and only in 9 per cent did infants and mothers reveal the same strain in the nose.

Table V *Resistance and Phage-type Analysis of the Strains of Staph. Aureus Isolated in the Infants and Their Mothers*

	C	D		E
	Infant	Infant	Mother	Infant = Mother
No. of strains	313	142	142	127
Penicillin resistant, %	82	79	42	56
Phage-group I, %	34	30	23	27

Table V shows the resistance/phage analysis of the last three groups in Table IV. Group C are children with negative mothers

Table II *Comparison Between Hospital Strains, i e Staph Aureus Isolated from Nurses in the Maternity Hospital, and Home Strains, i e Staph. Aureus Isolated from the Group without Direct Hospital Contacts*

Nasal Swabs in 1959	Hospital Strains (Nurses)	Home Strains: Infants Born at Home, On 7th Day	Home Strains: Infants Born at Home, At 1 Month	Home Strains: Mothers on Admission to Maternity Hospital
No of swabs	702	259	1,412	206
Staph aureus present number	287	117	582	45
Staph aureus present %	41	45	41	22
Penicillin resistant, %	89	32	43	33
Types 80 + 52/52A/80, %	16	7	6	6
Phage-group I, total, %	35	16	20	17
Phage-group II, %	19	30	29	30
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mothers seven days after delivery On the basis of the above-mentioned criteria, a distinct difference was revealed in the staphylococcal strains, harboured by infants and mothers Hospital strains were predominant among the infants and home strains predominated among the mothers

Table VI *Follow-up Studies at One Month of 878 Infants Born in the Maternity Hospital*

Nasal Swab on 7th Day in Maternity Hospital	No.	Nasal Swabs Taken at Home at One Month										
		Staph. Aureus Absent	Staph. Aureus Present					Penicillin-Resistant	Types 80+52/52A/80	Phage-Group I %	Phage-Group II	Phage-Group III
			A	B	C	Total						
						No.	%					
Staph aureus absent	547	354		34	159	193	35	68	9	33	27	18
Staph aureus present	331	77	196	6	52	254	77	76	12	34	26	21
Total	878	431	196	40	211	447	54	73	10	34	26	20

A *Strains identical with those isolated on the 7th day* B New strains identical with mother's, C New strains not identical with mother's

Penicillin resistance was present in 82 per cent, and 34 per cent of the strains belonged to Phage Group I, i e typical hospital strains

Analysis of the staphylococci in Group D showed that the strains from the infants had the characteristics of hospital strains, whereas those from their mothers were typical home strains

In Group E, i e infants and mothers with identical strains, the analysis showed a mixture of hospital and home strains, suggesting that both mothers and infants in some cases had been infected simultaneously by hospital strains

In order to clarify the extent to which mothers were infected during the stay in the Maternity Hospital, we studied 206 mothers both on admission and seven days after delivery Of these mothers, 62 per cent remained negative, 16 per cent were negative on ad mission, but became positive during the hospital stay, while 7 per cent who were positive on admission, had become negative at discharge, 4 per cent changed type from admission to discharge, while the type remained unchanged in 12 per cent 'Resistance/phage' analysis revealed 35 per cent penicillin resistant/17 per cent Group I on admission, while the corresponding figures at discharge were 44 per cent/19 per cent i e a shift towards hospital strains, parallel to the observed colonisation of a minority of the mothers

Our investigation thus confirms the results reported by others that infants born in a maternity hospital are colonised by hos pital' staphylococci to a much greater extent than by those carried by their own mothers

This phenomenon was further brought out by a follow-up examination at one month of 878 infants born in the Maternity Hospital In Table VI these infants are divided according to the results of the nasal swabs on the seventh day of life in the Maternity Hospital Of 547 who were negative at that time, 354 remained negative, 34 had acquired staphylococci identical to the strain present in their mothers, while 159 had acquired strains differing from those seen in their mothers A resistance/phage analysis of the 193 staphylococcal strains showed that 68 per cent were penicillin-resistant and 33 per cent were Group I strains These are typical hospital strains which the infants must have

Table VI *Follow-up Studies at One Month of 878 Infants Born in the Maternity Hospital*

Nasal Swab on 7th Day in Maternity Hospital	No.	Nasal Swabs Taken at Home at One Month										
		Staph. Aureus Absent	Staph. Aureus Present					Penicillin-Resistant %	Types 80+52/52A/80 %	Phage-Group I	Phage-Group II %	Phage-Group III
			A	B	C	Total						
						No.	%					
Staph. aureus absent	547	354		34	159	193	35	68	9	33	27	18
Staph. aureus present	331	77	196	6	52	254	77	76	12	34	26	21
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Table VII Follow-up Studies at One Month of Infants Born at Home and the Results of All Nasal Swabs Taken at One Month from Children Born at Home

Nasal Swabs on 7th Day at Home	N	Nasal Swabs Taken at One Month									
		Staph Aureus Absent	D	E	Total		Penicillin-Resistant	Types 80+52/52A/80	Phage-Group I	Phage-Group II *	Phage-Group III
					No.						
Staph aureus absent	133	97		36	36	27	31	0	9	39	19
Staph aureus present	108	43	49	16	65	60	35	2	14	34	20
Total	241	140	49	52	101	42	33	1	12	36	20
Total number of swabs at one month	1 412	830			582	41	43	6	20	29	22

D Strains identical with those isolated on the 7th day E Strains not identical with those isolated on the 7th day

carried home – either in the nose, though not detected by the swab, or elsewhere

The follow-up examination of 331 who were positive on the seventh day of life showed that 77 had lost their staphylococci, 196 had retained the same type, 6 had changed to the mother's type and 52 had a new type The analysis showed the same characteristics as the strains isolated during the hospital stay

Studies on Infants Born at Home

The nasal carrier rate is given in Table I, which shows that infants born at home are colonised to the same extent during the first week of life as those born in the Maternity Hospital On examination at the age of one month, the figures for infants born at home were the same as on the seventh day, while, as just shown, those for infants born in the Maternity Hospital were higher

The resistance/phage analysis of the staphylococci is given in Table II, which shows the difference from strains isolated in infants born in the Maternity Hospital (Table III)

The results of the follow-up examination at one month of 241 infants also studied on the seventh day of life, are shown in Table VII Of 133 who were negative at that time, 27 per cent acquired staphylococci in their noses This figure is lower than in the corresponding group of infants born in the Maternity Hospital (Table VI) The increase in the number of carriers practically equals the decrease, so that the percentage of nasal carriers remained on a constant level of about 40 No change occurred in the distribution of the strains as far as penicillin resistance and phage types were concerned

Studies on Sepsis

The 878 infants born in the Maternity Hospital and living in the district under consideration and the 1,412 infants born and living at home in the same district were studied by the health visitors for infections of the following character conjunctivitis typical pemphigus neonatorum, pemphigoid skin infections and a

Table VII Follow-up Studies at One Month of Infants Born at Home and the Results of All Nasal Swabs Taken at One Month from Children Born at Home

Nasal Swabs on 7th Day at Home	No.	Nasal Swabs Taken at One Month									
		Staph Aureus Absent	D	E	Total No.	Total %	Penicillin Resistant %	Types 80+52/52A/80	Phage Group I %	Phage Group II %	Phage Group III %
Staph aureus absent	133	97		36	36	27	31	0	9	39	19
Staph aureus present	108	43	49	16	65	60	35	2	14	34	20
Total	241	140	49	52	101	42	33	1	12	36	20
Total number of swabs at one month	1 412	830			582	41	43	6	20	29	22

D Strains identical with those isolated on the 7th day E, Strains not identical with those isolated on the 7th day

Table VIII *Clinical Infections in Infants Born in the Maternity Hospital and at Home Divided According to Sex and Type of Infection*

Place of Birth	Sex	No Examined	Conjunctivitis		Skin Infections		Other Infections		Total	
			No	%	No	%	No	%	No	%
Maternity Hospital	Male	468	20	4 3	45	9 6	1	0 2	66	14 1
	Female	410	20	4 9	39	9 5	2	0 5	61	14 9
	Total	878	40	4 6	84	9 6	3	0 3	127	14 5
At home	Male	717	35	4 9	77	10 7	0	0	112	15 6
	Female	695	25	3 6	46	6 6	3	0 4	74	10 6
	Total	1 412	60	4 2	123	8 7	3	0 2	186	13 2
Total		2 290	100	4 4	207	9 0	6	0 3	313	13 7

group comprising abscesses, whitlows and similar more deep-seated purulent infections, here classified as other infections Napkin area dermatitis, even when purulent, was not included in the skin infections In Table VIII, no distinction is made between typical pemphigus and pemphigoid skin infections, both being grouped together as skin infections

The *infections* observed in these 2,290 infants are shown in Table VIII The figures in the Table are similar to those from 1956 and 1957 mentioned in the introduction, both for infants born in the Maternity Hospital and for those born at home As no staphylococcal epidemics occurred during the period under investigation we believe that *the figures disclosed, i e 13–15 per* cent indicate the endemic level for superficial pyogenic infections in infants during the first two months of life

It is seen from Table VIII that purulent conjunctivitis occurred in about 4 5 per cent and purulent skin infections in 9–10 per cent of the infants More serious infections particularly abscesses, were rarely encountered

The figures how that the frequency of infections was probably a little higher in infants born in the Maternity Hospital than in those born at home The sex differences in the frequency of infections are more striking than the differences between infants born *in* the Maternity Hospital and those born at home

Table IX *Distribution of the Infection According to Time of Onset*

Place of Birth	Week of Life in Which Infection Started								No Information
	1st	2nd	3rd	4th	5th	6th	7th	8th	
Maternity Hospital	23	28	48	22	2	1	0	2	1
At home	39	57	59	23	5	1	1	2	8
Total	53	85	107	45	7	2	1	4	9
%	18	28	35	15	2	1	–	1	–

The onset of the infections according to the week of life is given in Table IX the maximum is seen to occur in the second and third weeks of life just as shown in Fig 1 Only 4 per cent of the infections occurred after the first four weeks of life

Table X *Frequency of Infections in Infants Living in Urban and Rural Districts*

Place of Birth	Urban District			Rural District		
	No Examined	Infection Present No	%	No. of Cases	Infection Present No.	%
Maternity hospital	526	92	18	352	35	10
At home	703	110	16	709	76	11

Table X shows the frequency of infections in infants living in the city of Aarhus and in the surrounding rural district The frequency is distinctly higher in the urban district, both in infants born in the Maternity Hospital and those born at home, which suggests that the environment plays a role

Table XI *Relation Between Results of Nasal Swabs and Swabs from Clinical Infections in Infants Born in the Maternity Hospital and at Home*

Nasal Swabs on Seventh Day	Nasal Swabs at One Month					
	Staph Aureus Absent			Staph Aureus Present		
	No. Examined	With Infections No	%	No. Examined	With Infections No	
Maternity Hospital						
Staph aureus absent	354	35	10	193	25	13
Staph aureus present	77	13	17	254	54	21
Total	431	48	11	447	79	18
At home						
Staph aureus absent	97	9	9	36	4	11
Staph aureus present	43	4	9	65	8	12
Total	140	13	9	101	12	12
All infants born at home	830	90	11	582	96	17
Total	1 261	138	11	1 029	175	17

The role of the initial infection, i e the nasal infection in the first week of life, is analysed in Table XI which shows that the infants whose nasal swabs were negative on the seventh day of life had the lowest frequency of clinical infections The highest

frequency was seen in infants who were positive both at the end of the first week of life and at the age of one month In addition, the Table shows that infants who had negative nasal swabs during the entire period of examination sometimes had clinical infections

Table XII Number and Percentage of Cultures with Staph Aureus from Clinical Infections

Place of Birth	No of Infections	No Cultures performed	Cultures from the Infections					Cultures with Staph. Aureus	
			Within 1st Week after Onset		Later than 1st Week after Onset		Total	No.	%
			Negative	Positive	Negative	Positive			
Maternity Hospital	127	25	18	45	19	20	102	65	65
At home	186	42	37	54	31	22	44	76	53
Total	313	67	55	99	50	42	246	141	57

The results of cultures from the recorded infections are given in Table XII which shows that cultures were performed in 246 of the 313 infections (80 per cent) It is seen that Staph aureus was isolated with a relatively higher frequency in the cases where the swabs were obtained within the first week after the onset of the infection than in those in which the swabs were taken at some later time But even in the latter group positive cultures were obtained and Staph aureus was revealed in 57 per cent of the cases studied

Cultures were performed in 79 of the 100 cases of purulent conjunctivitis in 24 per cent Staph aureus was isolated In all cases with positive nasal swabs identical types were isolated from the eyes and nose of the same infant.

Cultures were made in 166 of the 207 cases of skin infections, 79 per cent of these were positive Agreement with the positive nasal swabs was seen in 64 per cent of the cases while in 36 per cent i e 29 infants the type of staphylococci harboured in the nose differed from that isolated from the infection

Table XIII shows the results of a resistance/phage analysis of staphylococci isolated from infections in infants born either in

Table XIII *Resistance and Phage-Type Analysis of Strains Isolated from Clinical Infections*

Place of Birth	No. of Positive Cultures	Penicillin-Resistant %	Types 80 + 52/52A/80 %	Phage-Group I %	Phage-Group II %	Phage-Group III %
Maternity hospital	65	79	18	46	26	15
At home	76	58	12	17	26	24

the Maternity Hospital or at home A comparison with the figures listed in the bottom row in Tables VI and VII shows (i) that the staphylococci isolated from infections in infants born in the Maternity Hospital had nearly the same penicillin resistance as their nasal staphylococci, (ii) that the percentages of Phage Group I and of types 80 + 52/52A/80 are higher among the staphylococci isolated from infective lesions than in the nasal strains, and (iii) that these two figures are higher than the corresponding figures among the hospital strains judged by the nasal swabs from the nurses (Table II)

In infants born at home, the strains isolated from infective lesions revealed a higher rate of penicillin resistance (58 per cent) than did their nasal strains (43 per cent) Phage Group I comprised 17 per cent of the strains from infective lesions, including 12 per cent of types 80 + 52/52A/80 The corresponding figure from the nasal swabs was 6 per cent

This analysis suggests that the infections are principally due to penicillin-resistant staphylococci, and that types 80 + 52/52A/80 play a considerable role, both in infections in infants born at home, in whom these types are relatively rare in the nose, and in infants born at the Maternity Hospital, where they occur more frequently

However, the figures are too small for definite conclusions as to the specific role played by special phage types, but nevertheless there seems to be a relationship between penicillin resistance and infections

Discussion

A thorough discussion of the many papers on staphylococci in maternity hospitals published during recent years will not be

presented here The reader is referred to the papers publishead by Elek (1959) and Williams et al (1960)

Our investigation on nasal colonisation in newborn infants in the State Maternity Hospital for Jutland was prompted by the study performed by Gillespie et al (1958) in the Bristol Maternity Hospital in 1955–1957 These investigators found that 80–90 per cent of the infants were colonised by Staph aureus at the end of the first week of life, corresponding to an infection rate of 25 per cent per day In Bristol the introduction of a hexachlorophene regimen resulted in a reduction in the spread of infections but the nasal carrier rate was still about 60 per cent on the seventh day of life

In March to December 1959, we constantly found a nasal carrier rate of about 40 per cent at the end of the first week of life among the infants born in the Maternity Hospital i e an infection rate of 8 per cent per day Hexachlorophane or other antiseptics were not used but strict aseptic precautions were taken

In control studies on infants born at home we found a similar infection rate i e 8 per cent per day As far as the period under investigation is concerned it may therefore be concluded on the basis of the nasal swabs that the risk of staphylococcal colonisation is the same whether the infant is born at home or in the Maternity Hospital

An evaluation of this risk on the basis of an analysis of the frequency of superficial pyogenic infections during the first two months of life gave the same result i e that the sepsis rate in the infants born in the hospital was similar to that in infants born at home i e 13–15 per cent

Staph aureus was isolated in 57 per cent of the infections which were subjected to bacteriological studies

The relation between clinical infections and the results of nasal swabs showed that the frequency of infection was higher among infants who were nasal carriers than among those who were not carriers In the cases where Staph aureus was isolated both from the nose and from a skin infection in the same infant identity was revealed in only 65 per cent while strains isolated in infants with conjunctivitis were identical with the nasal strains in all cases.

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Discussion

A thorough discussion of the many papers on staphylococci in maternity hospitals published during recent years will not be

The features of the hospital strains are that more than 30 per cent of them belong to Phage Group I, and that more than 65 per cent are penicillin resistant, while less than 20 per cent of the home strains belong to Phage Group I and less than 45 per cent of these are penicillin resistant

Most nasal carriers among infants born in the Maternity Hospital were colonised by hospital strains Only a few (9 per cent) acquired types identical with those of their mothers Carriers among mothers on admission harboured home strains

Control studies at one month showed that infants colonised in the Maternity Hospital retained their hospital strains Infants who were negative at discharge revealed nasal staphylococci in 35 per cent at one month These strains also had the features of hospital strains

Staphylococci isolated from infants born at home had the characteristics of home strains both at the age of seven days and one month

Pyogenic infections of the skin and conjunctivæ occurred in 13-15 per cent of the infants within the first two months, with a maximum in the second and third weeks of life

Bacteriological studies on these infections revealed Staph aureus in 57 per cent of the cases

Clinical staphylococcal infections occurred in 313 infants Among these, nasal swabs obtained at the age of one month were negative in 138 and positive in 175 The latter revealed identical types in the nose and on the conjunctivæ in all cases of bacterial conjunctivitis while the type isolated from the inflammatory process was identical with the nasal strain in only 65 per cent of the skin infections

Nasal swabs obtained in a large group of newborn infants make it possible to characterise the staphylococci present in the environment in which the infant is born and lives in the neonatal period but they do not give a definite expression of the individual risk of contracting staphylococcal infections

A negative nasal swab does not exclude the possibility that the infant is a staphylococal carrier

Among the 313 infants with clinical infections, 175 were nasal carriers of Staph aureus In the remaining 138, staphylococci could not be isolated from nasal swabs taken at the age of one month

Accordingly, it seems that studies on nasal carriage of Staph aureus in newborn infants are not of unquestionable value in the assessment of the risk of contracting staphylococcal infections

On the other hand, phage typing and determination of resistance of the strains of staphylococci isolated in the infants are of great value, because these investigations make it possible to define the bacteriological environment into which the infants are born

A single nasal swab does not definitely reveal whether or not the infant has acquired staphylococci Among 547 infants with negative nasal swabs on discharge from the Maternity Hospital, 193 revealed nasal carriage of staphylococci after a three weeks' stay in their homes Analysis of the staphylococci in these 193 cases rendered it likely that they had been acquired in the Maternity Hospital and not in their homes We cannot say anything as to the of location of the staphylococci at the time of the negative nasal swabs, but it is reasonable to assume that they were on the skin or the umbilicus, as observed by Gillespie *et al* (1958)

Accordingly, a single negative nasal swab does not exclude the possibility that the infant is a staphylococcal carrier, only a positive culture gives definite information about this point

Summary and Conclusions

Nasal swabs obtained on the seventh day of life revealed that 40 per cent of 1,577 infants born in the State Maternity Hospital for Jutland and 45 per cent of 259 infants born at home were carriers of Staph aureus

Analysis of the phage types and penicillin resistance revealed two well defined groups (i) 'hospital strains with the characteristics of strains isolated from nurses in the Maternity Hospital and (ii) home' strains, with the characteristics of strains isolated from infants born at home

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From the Department B (Professor E Brandstrup) The Royal Maternity Hospital, Copenhagen Denmark

PERINATAL NON SPECIFIC PNEUMONIA

BY

HANS J MØLLER

After Jorg in 1835, had distinguished between atelectasis and pneumonia in the newborn no particular interest was displayed in perinatal pneumonia for some time About 1880, the diseases which might occur in the newborn infants of infected mothers were becoming better understood von Hecker (1876), Geyl (1880) and Silbermann (1884) on the basis of the literature as well as their own experiments and clinical findings, pointed out that pneumonia in the newborn might be due to aspiration of infected matter from the birth canal

A distinction is made between congenital pneumonia acquired *in utero* and post natal pneumonia, congenital meaning cases found in stillborn as well as in live-born babies dying within three days of birth (Hess Thaysen 1914, Johnson and Meyer, 1925 Morison 1952)

Hess Thaysen, in 1914 described four main types of pneumonia in newborn infants These types are found with certain modifications in most subsequent publications and will also be used here

(1) *Placental infections* including syphilitic and tuberculous infections and in addition certain rare cases of streptococcal and staphylococcal and pneumococcal pneumonias, and in recent years also listeriosis (Luttor, 1958 Hauge Kristensen, 1960) On the basis of the literature animal experiments, and a clinical series of cases Hellendall (1906) demonstrated that

Acknowledgment

Our thanks are due to dr Kirsten Rosendal, The State Serum Institute, Copenhagen, for performing the phage groupings

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consider Cruickshank s (1930) atelectatic pneumonia and MacGregor s (1939) corresponding types Both authors stress the significance of pulmonary function in the pathogenesis and development of pneumonia Incomplete expansion of the lung or other pulmonary changes (bleeding, membrane formation, etc), and diminished respiration due to damage to the respiratory centre will increase the risk of pneumonia It is emphasized by MacGregor that asphyxia at birth with the consequently depressed respiration will partly inhibit the normal expansion of the lungs and partly depress the cough reflex and thus increase the risk of pneumonia

As already mentioned pneumonias have been found caused by pneumococci, streptococci, and staphylococci Studying a large series by Gram staining of sections and culture from the pulmonary tissue MacGregor found these organisms as well as others, such as E coli, H influenzæ, and enterococci Nevertheless, there were cases in which, despite a careful study, no micro-organisms were found to account for the pneumonia Some of these cases may have been caused by aspiration of non infectious matter such as gastric contents In addition to the above mentioned bacteria which are relatively common, other rare causes have been reported *e g* listeria (Wiener, 1957 Luttor, 1958, Hauge Kristensen and Jessen, 1960), Monilia albicans (Benirschke 1958 Flamm 1959), and viruses (Adams, 1948 Flamm, 1959)

The reported frequency of pneumonia in the newborn differs widely some authors including only stillborn while others also include live-born infants Moreover the length of the defined neonatal period has varied Certain authors have included all cases of inflammatory changes of the lungs and others only cases in which the pneumonia has been considered an important factor In order to accept a series, microscopic examination of the lung tissue must be demanded (Morison, 1952 Potter, 1952) Thus Hess Thaysen stated that while pneumonia had been *diagnosed in 8 per cent* of the newborn infants prior to his study 42 per cent were found to have pneumonia in a corresponding series by microscopic examination

MacGregor (1939) found pneumonia in 11 per cent of still

the fœtus might be infected by maternal sepsis and *by spread of* intra-peritoneal infective conditions to the genitalia (Müller, 1956) Furthermore, there have been a number of case reports of *definitely* congenital pneumococcal pneumonia in which pneumococci of the same type have been found in mother and fœtus MacDonald, 1911, Gordon and Lederer, 1928, and others Niederhoff (1909), reported a case of streptococcal pneumonia due to maternal sepsis

(2) *Aspiration pneumonias* comprise those due to aspiration of infected matter from the birth canal as well as those due to aspiration of milk, gastric contents, etc As is well known, maternal infection is commonly seen in prolonged labour Risacher (1928) studied the bacterial content of the amniotic fluid Three hours after the rupture of the membranes infection was present in 50 per cent of cases, and at the end of ten hours only a few remained uninfected These results have been confirmed by several subsequent authors who have also demonstrated the same bacteria in the nasopharynx of the infants (Gosselin, 1937, Cornelison *et al*, 1946, Ferrario, 1952) In autopsy series Douglas *et al* (1943) and Arey and Dent (1953) demonstrated that prolonged deliveries were attended by an increased incidence of pneumonia among the infants that succumbed neonatally Hellendall as well as Muller found that ascending infection might occur despite intact membranes In addition, it is worth emphasizing the possibility of ill effects from aspiration of highly irritating substances used to clean the birth canal

(3) *Aerogenous pneumonias* This variety is most apt to occur as epidemics in the premature wards, but occasionally isolated cases have also been reported (Abramsen, 1949, Briggs, 1957, Donald and Cocker, 1957)

(4) *Metastatic pneumonias*, originating from other sources of infection, such as primary intestinal disease, infections of the umbilicus, or other external cutaneous lesions This type Hess Thaysen considered rare, but in this group as well as in the preceding one the staphylococcal problem must be borne in mind (Abramsen, 1949, Briggs, 1957 Timbury, *et al*, 1958)

This classification is based on ætiology and is generally accepted In order to arrive at a better understanding, it is helpful to

Table I *Composition of Series*

Birth Weight in g	Live Born		Stillborn	
	Total	With Pneumonia	Total	With Pneumonia
under 1 000	13	5	0	
1 000–1 500	34	8	6	
1 500–2 000	24	4	4	
2 000–2 500	11	2	7	2
over 2 500	9	2	12	1
	91	21	29	3

Table II *Interval between Rupture of the Membranes and Delivery*

	Live-born		Stillborn		Total	
	Total	With pneumonia	Total	With pneumonia	Total	With pneumonia
under 24 hours	65	12	23	1	88	13
over 24	26	9	6	2	32	11

and mild changes, (b) *moderate* comprising cases with scattered, more pronounced lesions, and (c) *severe* with severe diffuse changes The next column gives the cause of death, an attempt being made in each case to ascertain the probable cause of death The last column gives comments of possible interest

The clinical picture was uniform and typical, showing the well known state of respiratory distress Pneumonia was not diagnosed clinically in any case The time of death is shown in Table IV

Discussion

The series is somewhat selected as the cases admitted to the Departments were mainly complicated Some may have been in labour for some time or may have been primarily infected It must be assumed therefore that the 24 (20 per cent) cases of perinatal pneumonia represent a maximum value and that larger, less selected series will show fewer cases

born and 18 per cent of live-born babies dying within the first week of life This accords reasonably with the values stated by Johnson and Meyer (1925), Warwick (1934), Chase (1935), and Morison (1952) In a Swedish series from 1955, Kjessler found 70 cases of pneumonic changes among 397 neonatal deaths The extremes have been reported by Helwig (1933) who found 41 5 per cent and Valle (1952) who found 4 3 per cent Bundesen's 7 per cent from 1955 has to be regarded with some reserve, since his was a large collected series in which the extent of post mortem investigation was highly varied

Clinically, neonatal pneumonia does not differ from other pulmonary changes, such as hyaline membranes, bleeding, and simple atelectasis Their presentation is identical respiratory distress Either immediately after birth or after an interval of a few hours, the infants develop increasing dyspnœa, alternating with attacks of apnœa They have attacks of cyanosis, increasing to permanent cyanosis In addition, there may be trembling, possibly convulsions, and unilateral change of colour The fully developed syndrome shows a pale, cyanosed infant with severe dyspnœa, rales, and retractions in the chest Sometimes sudden death from pneumonia may occur (Jacobsen and Voigt, 1956), but as a rule the baby succumbs in a state of increasing respiratory and cardiac failure

Present Series

The present series comprises 120 infants from the Maternity Departments of the University Hospital, Copenhagen, – 29 stillborn and 91 live born dying within the first few days of life Microscopic examination of all five lobes of the lungs was carried out in all cases All inflammatory changes were accepted as signs of pneumonia Bacteriological studies were not performed

The composition of the series is shown in Table I

The significance of the interval from the rupture of the membranes until delivery was investigated (Table II)

A schematic representation of the individual cases is shown in Table III Maternal complications, if any are recorded The pneumonias were divided into three degrees (a) *Slight*, incipient

entation of the Clinical Picture

Degree of Pneumonia	Cause of Death	Comments
Slight	Intra-cranial hæmorrhage	
Slight	Immaturity	Hydrorrhœa 14 days
Moderate	Immaturity	
Slight	Intra-uterine asphyxia	
Severe	Pneumonia	Hydrorrhœa 14 days
Moderate	Immaturity	
Severe	Immaturity + pneumonia	
Moderate	Atelectasis + pneumonia	
Slight	Immaturity	Habitual abortion progesterone treatment
Slight	Intra-cranial hæmorrhage	Aspiration pneumonia
Severe	Pneumonia	Acute meningo-encephalitis
Slight	Pulmonary hæmorrhage atelectasis	
Moderate	Pneumonia prematurity	
Severe	Prematurity pneumonia	
Moderate	Asphyxia	
Severe	Prematurity hyaline membrane pneumonia	
Slight	Intra-cranial hæmorrhage hyaline membrane	Hydrorrhœa 13 days
Severe	Intra uterine asphyxia	Hydrorrhœa 14 days
Moderate		Hydrorrhœa 2 — 3 days
Slight	Intra-cranial hæmorrhage	
Moderate	Intra-uterine asphyxia	
Slight	Asphyxia	Hydrorrhœa 4 days
Severe	Pneumonia	
Slight	Hyaline membrane	Cæsarean section contaminated amniotic fluid

tween primary and secondary atelectasis A thorough study of perinatal deaths therefore must include microscopic examination of the lungs

As already mentioned, pneumonia in stillborn infants and infants succumbing within the first three days of life was classified

Table III *Schemann Rep*

No.	Sex	Weight	Condition at Birth	Death after Hours	Duration of Labour	Maternal Complications
4	F	1 050	Alive	36	14	Anaemia ulcerative colitis
8	F	600	Alive	1	Hydrorrhoea for 14 days	
11	M	700	Alive	48	48	
13	F	2 700	Dead		14	Infection
14	M	1 250	Alive	59	15	
15	M	800	Alive	54	4	
17	M	700	Alive	16	17	
19	M	1 300	Alive	38	48	
26	F	900	Alive	48	5	
30	M	1 300	Alive	55	14	
31	M	1 400	Asphyxiated	7 days	8	Toxaemia
36	F	1 900	Alive	24	9	Toxaemia
38	F	1 150	Asphyxiated	106	30	
39	M	1 050	Asphyxiated	12	7	
40	F	3 950	Asphyxiated	1/4	25	Infection
57	M	1 350	Alive	24	3	
69	M	1 850	Alive	5	8	Infection
77	F	2 400	Dead		[illegible]	Infection
79	F	1 600	Alive	1	4	Infection
93	M	3 900	Alive	15	8	Severe cholangitis
96	F	- 300	Dead		34	Infection
99	M	2 000	Asphyxiated	1 2	10	Infection
115	F	1 850	Alive	11 days	41	
119	M	2 050	Alive	40	18	Transverse position

The diagnosis of pneumonia was not made in any case at the time of routine autopsy, but only when microscopic examination was performed This emphasizes the significance of microscopic study, which is also required in order to make a diagnosis of hyaline membrane, pulmonary bleeding, and to distinguish be-

before delivery In one case (93) it may be assumed that the infection was transplacental, the mother having septic cholangitis This leaves 4 cases which are not directly explained, including one (36) showing, in addition to the pneumonic changes, acute meningo-encephalitis

During the second day of life, 5 infants died of pneumonia In Case 4 there was a possibility of infection during birth, since the birth canal may have been contaminated as a result of the mother s disease (ulcerative colitis) In Case 11 maternal infection was present, so this case like No 19, was classed as congenital, since the fairly severe changes could hardly have developed in the thirty six hours of extra uterine life One baby (No 26) was premature weighing 900 g After doing well for the first few hours deterioration occurred As autopsy showed only slight changes, it was considered that the pneumonia developed after birth Case 119 had mild changes Since maternal infection was present and tracheal suction had been performed after birth it was assumed that the infection had occurred in the course of delivery

Three infants died of pneumonia in the third day of life In one of the cases (No 14) the changes were so severe that the pneumonia must have been of intra uterine origin (Fig 1) Hydrorrhœa had been present for two weeks prior to delivery

Case 15 had moderately severe changes There was some question of self induced premature delivery with consequent infection but the possibility of post natal infection could not be ruled out In Case 30 the changes were mild and the cause of death was intra cranial injury Presumably because of this injury, combined with prematurity respiration was impaired, and the baby was thus prone to pulmonary infection

Three infants died later than the third day of life One had aspiration pneumonia (Case 31) while in the other 2 Cases no cause was found (Cases 38 and 115) but both were premature and therefore had reduced resistance

There was no case of metastatic pneumonia and there was also no aggregation of cases at any period of time, indicating an epidemic The great majority of the infants were premature there being only 3 term babies However, among the live-born there

Table IV *Time of Death*

	Total Deaths	With Pneumonia
First 24 hours	48	10
First 48 hours	18	5
First 72 hours	12	3
Later	13	3
	91	21

as congenital This is generally correct, but there are exceptions In several instances, the infection was almost certainly secondary to resuscitation manœuvres at the time of birth In the presence of severe, diffuse changes, it seems reasonable to interpret the cause as congenital, but scattered and mild changes may be due to infection acquired after birth Thus, Allinson (1958) has emphasized the importance of keeping the early environment as clean as possible In addition, Moller-Madsen *et al* (1959) have demonstrated the significance of performing tracheal suction by a technique as gentle as possible, using sterile instruments The ordinary sucker is frequently of the ejector type and therefore involves another possible source of infection, since the current of air ejected from it may be infected In administering oxygen the instruments have to be sterile (Dons *et al*, 1959) In prematures and infants with impaired respiration, an attempt is often made to clear the air passages This process involves considerable danger of infecting the baby, if the risk is not realized

In the light of these facts, an attempt was made to assess the 24 cases of pneumonia in respect to origin, congenital or acquired after birth

The 3 cases in the stillborn infants (13, 77, and 96) were obviously congenital Maternal infection was present in all 3

During the first twenty four hours of life, 10 infants succumbed to pneumonia All these cases were classed as congenital, since in most of them death occurred soon after birth The changes in this group were so severe that the lesions could hardly have arisen after birth In 4 instances (40, 69, 79, and 99) there had been signs of maternal infection, in one case hydrorrhœa for two weeks

over, infants who have been asphyxiated at birth and who have been resuscitated by tracheal intubation, run a certain risk of developing respiratory infections Infants with impaired pulmonary function are also particularly exposed. In the event of an epidemic of infection among mothers and infants in the ward (which was not the case in the present series), some of the infants may acquire pneumonia as a consequence of this In such instances, there is the possibility of metastatic pneumonia, but aerogenous pneumonia may also occur

SUMMARY

The literature on neonatal pneumonia is reviewed and a series comprising 91 infants who died during the neonatal period and 29 who were stillborn is described Among these infants 21 and 3 respectively showed pneumonia histologically

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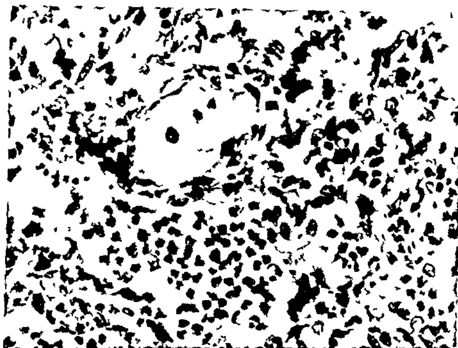


Fig 1 Photomicrograph of lung from premature infant with pneumonia (Case 14)

were 6 in the weight group 1,500–2,500 g, and given optimal conditions such infants have a fair chance of survival to-day

Thirteen infants weighed less than 1,500 g including 5 under 1,000 g In some of the cases maternal infection may have been responsible for the premature delivery In these cases, as well as those in which infection occurred later, the pneumonia could have been acquired during or immediately after birth, possibly related in some to impaired pulmonary function and reduced resistance

As already stated the series is a selected one, but it does show clearly that neonatal pneumonia is a factor of importance in perinatal mortality The diagnosis cannot always be made by clinical method, but empirically it can be said that about 20 per cent of infants with respiratory distress are suffering from pneumonia By assessing the history of the delivery etc a probability diagnosis may be made For instance the risk of pneumonia is greatest in cases of maternal infection or prolonged labour More

Ra ımo L. G ınoos M and Ki ko ki A Acta obst. et gynec. Scandinav 40 321 1961

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A COMPARATIVE STUDY OF THE OBSTETRICAL HISTORY OF PUPILS IN SCHOOLS FOR BACKWARD CHILDREN AND ELEMENTARY SCHOOL PUPILS

BY

L RAURAMO M. GRÖNROOS AND A KIVIKOSKI

In the present view the proper task of schools for backward children is to teach mentally retarded children (and borderline cases) who fail to qualify for ordinary elementary school They also deal with individuals who for some reason find ordinary schooling difficult and are therefore relegated to such a school In these circumstances it does not necessarily follow that the pupil is backward (Mäki, 1951) Obstetricians take a constant interest in the possible role of various complications of labour in the genesis of retarded cerebral development One way of studying this question is to compare the obstetric case records of pupils at schools for backward children and those at elementary schools In Finland this problem has been studied *e g* by Brander (1936) and Parviainen (1945, 1946) Parviainen was especially concerned with the prognosis for premature babies, as assessed by means of intelligence tests He found that early rupture of the membranes during labour which shortened its duration improved the prognosis Brander studied the delivery reports of 101 pupils of schools for backward children and found four times more premature births among the backward pupils

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The elementary school series was selected in accordance with the same criteria as the backward children group Consequently it too, includes only the cases whose delivery reports could be checked at the maternity hospitals

Results

Table I gives some data of a general nature on the structure of the series The two groups are fairly homogeneous as regards the mean age of the parturients and the mean weight of the babies On the point of marital status however, eleven times as many unmarried mothers were found among the mothers of backward children The authors consider that this is indicative of Māki s (1951) conclusion regarding the role of hereditary and environmental factors in the causation of retarded mental development Viewed against the socio economic background it seems natural that the relative proportion of unmarried mothers should be large in the backward school series

Table I *Data of a General Nature on the Structure of the Series*

Groups	Total		Marital Status of the Mothers		Mean Age of the Mothers Years	No. of Primi gravidae	No. of Multi parae	Mean Weight of the Children g
	Boys	Girls	Married	Unmarried				
Pupils in school for backward children	93	49	120	22	28 3	56	86	3226
Elementary school pupils	93	49	140	2	28 9	52	90	3470

In Table II the possible effect of the child s birth weight is examined The incidence of prematurity is eight times greater in the backward school series than in the controls Obstetricians will be gratified to know on the other hand, *that the proportion of children of high birth weight attending schools for back ward children was not greater than expected* Indeed the proportion of children weighing over 4 kg at birth in the backward series was approximately half that in the control series *The present series differs in this respect from* B r a n d e r s *(1936)*

than among the normal school population He thought that schools for backward children included an unusually large proportion of children with a greater than average birth weight Compared with the general incidence, breech deliveries were twice as frequent among the backward pupils, and breech extractions were more than five times as frequent It was also possible to establish a higher incidence of high forceps deliveries and twin pregnancies in the history of the backward pupils Since Brander's investigations there have been profound changes in the management of labour and these changes have led to an improvement in the prognosis for the children delivered One feature of this trend, is that, according to Rauramo (1954), the incidence of Cæsarean sections in Finland was 8 5 per 1,000 in 1937 to 1941 and 25 6 per 1,000 in 1947 to 1951 Maternal mortality from Cæsarean sections has dropped markedly At the Women's Clinic, University of Turku, for instance, the maternal mortality from Cæsarean section in 1938 to 1946 was 0 43 per cent of all parturients, while in 1947 to 1951 the corresponding figure was only 0 07 (Rauramo, 1952) It is of interest to find out whether the changes in the management of labour towards greater consideration for the interests of the child have altered, since the time of Brander s investigation, the proportion of bad obstetric histories among pupils in schools for backward children To this end, data were collected on the pupils in schools for backward children born in Turku in 1936 to 1951 and the incidence of complications of labour in this series compared with the incidence in normal elementary school children

The Series

The series consisted of two groups

(1) Pupils in schools for backward children, 142 in all, born in 1936 to 1951, selected from the register of the Turku School for backward Children, whose delivery reports the authors were able to obtain

(2) The elementary school group which comprised as many girls and boys each year as the backward-school series and in which all pupils had completed at least the III grade syllabus

The elementary school series was selected in accordance with the same criteria as the backward children group Consequently it, too, includes only the cases whose delivery reports could be checked at the maternity hospitals

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Table II *Distribution of Premature Babies and Large Babies*

Groups	Children Weighing ⋜ 2 500 g at Birth	Children Weighing ⋝ 4 000 g at Birth	No of Twin Pregnancies
Pupils in school for backward children	16	9	5
Elementary school pupils	2	17	2

findings which suggested that children who had been overweight at birth formed an abnormally high proportion of those attending schools for backward children

Table III shows the incidence of certain types of operative delivery Forceps and breech deliveries were approximately twice as frequent among the backward pupils as in the control series Cæsarean sections, on the other hand, were more numerous in the control series Brander reported an incidence of 11 9 per cent for breech presentations, compared with 6 3 in the present backward children series As has been shown by Rauramo (1950), the increased use of Cæsarean section for breech pre sentation has resulted in a considerable decrease in perinatal mortality It would seem from the above figures that although the incidence of forceps and breech deliveries continues to be slightly higher in the backward-school children than in normal series, the proportion is smaller than in Brander's series (the forceps incidence was 5 per cent in Brander's and 2 8 per cent in the present series)

Table IV shows the incidence of toxæmia and asphyxia in the present series All forms of toxæmia were more frequent among

Table III *Incidence of Certain Operative Deliveries*

Groups	No of Cæsarean Sections	No of Forceps Deliveries	No of Breech Deliveries
Pupils in school for backward children	2	4	9
Elementary school pupils	4	2	4

the backward school children than in the normal series Asphyxia, on the other hand, had roughly the same incidence in both series Asphyxia was diagnosed on the basis of signs noted during labour (colour of amniotic fluid, complications of the umbilical cord, and variation of fœtal heart sounds) The delivery reports made no mention of the condition of the baby immediately after birth Thus the role of asphyxia could not be fully assessed in the present series Nevertheless the equally great frequency of asphyxia diagnoses is in itself noteworthy

Table IV *Incidence of Toxæmia and Asphyxia*

Groups	Eclampsia No of Cases	Severe Pre eclampsia, No of Cases	Mild Pre eclampsia, No of Cases	Signs of Asphyxia No. of Cases
Pupils in school for backward children	1	7	14	20
Elementary school pupils	–	1	10	19

The duration of labour was statistically significantly (P = 0 05) longer in the backward school series than in the controls The total duration of labour was 18 2 ± 1 5 hours in the backward school series and 13 7 ± 0 8 hours in the elementary school series Fig. 1 gives the cumulative incidence of labours in different time groups

Using the formula

$$s\ (F_1) = \sqrt{\frac{F_1\ (1 - F_1)}{n}}$$

it can be shown that labours under 18 hours occurred in the backward school series in 62 6 ± 4 1 per cent and in the elementary school series in 77 3 ± 3 5 per cent and labours under 24 hours correspondingly in 75 6 ± 3 6 per cent and 88 7 ± 2 7 per cent Labour longer than 18 or 24 hours occurred significantly (P = 0 05) more often in the backward school series than in the elementary school series There was no difference in the incidence of very short labours between these groups In our series there were only two labours of more than 60 hours duration (111 and

Table II *Distribution of Premature Babies and Large Babies*

Groups	Children Weighing $\leq$ 2,500 g at Birth	Children Weighing $\geq$ 4,000 g. at Birth	No. of Twin Pregnancies
Pupils in school for backward children	16	9	5
Elementary school pupils	2	17	2

findings which suggested that children who had been overweight at birth formed an abnormally high proportion of those attending schools for backward children

Table III shows the incidence of certain types of operative delivery Forceps and breech deliveries were approximately twice as frequent among the backward pupils as in the control series Cæsarean sections, on the other hand, were more numerous in the control series Brander reported an incidence of 11 9 per cent for breech presentations, compared with 6 3 in the present backward children series As has been shown by Rauramo (1950), the increased use of Cæsarean section for breech presentation has resulted in a considerable decrease in perinatal mortality It would seem from the above figures that although the incidence of forceps and breech deliveries continues to be slightly higher in the backward school children than in normal series the proportion is smaller than in Brander s series (the forceps incidence was 5 per cent in Brander s and 2 8 per cent in the present series)

Table IV shows the incidence of toxæmia and asphyxia in the present series All forms of toxæmia were more frequent among

Table III *Incidence of Certain Operative Deliveries*

Groups	No of Cæsarean Sections	No of Forceps Deliveries	No. of Breech Deliveries
Pupils in school for backward children	2	4	9
Elementary school pupils	4	2	4

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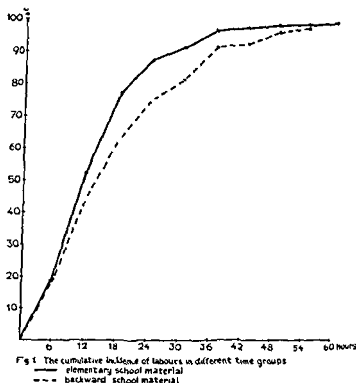


Fig 1

148 hours, respectively) Both of these were pupils in the school for backward children Brander's (1936) premature series did not show that the duration of labour endangered the baby According to Parviainen (1945), on the other hand, early rupture of the membranes which shortened the duration of labour, improved the prognosis for premature babies

Table V shows the drugs used during labour The backward school group shows a greater number of mothers given oxytocics

Table V *Use of Drugs*

Groups	Oxytocics No of Cases	Morphine or Derivatives No of Cases
Pupils in school for backward children	11	4
Elementary school pupils	5	3

or morphine or its derivatives in labour This is as expected for in Finland both drugs are mostly used in labour which are more protracted than normal and the duration of labour in the backward school group was longer than in the control series

Discussion

Comparison of the obstetric history of pupils in a school for backward children with that of elementary school children showed that most complications of labour were more frequent in the former group It was especially noted, however, that an abnormally high birth weight was rather less common in the backward-school than in the elementary school series The previously established high rate of prematurity among the pupils in schools for backward children was confirmed by the present study *The duration of labour in the backward school series was significantly longer than in the elementary school series* It is consequently somewhat surprising that the incidence of symptoms of asphyxia during labour was about the same in the two groups However, as the post natal condition of the babies was not detailed in the delivery reports no definite conclusion should be drawn from this observation It is also questionable whether the high incidence of unmarried mothers among the backward series compared with the elementary school series can be regarded as an obstetric factor It is true that inadequate maternity care is more common among unmarried parturients but it would seem that the main influence in this group is by way of later environmental factors or hereditary factors It is very probable that children of unmarried mothers receive inferior treatment later and are more exposed to various detrimental environmental influences *Judging by the present study the child that might be considered most likely to become a candidate for a school for backward children is the premature child of an unmarried mother who had toxæmia of pregnancy whose labour was prolonged and was treated by the administration of oxytocics and terminated in either breech or forceps delivery*

As series of this type are naturally small it is difficult to draw mathematically reliable conclusions on the influence of all the

factors considered on the subsequent intellectual development of the children The differences are surprisingly clear, however, with certain complications, both in the present and in some earlier investigations We are of the opinion that more attention should be paid to the possible detrimental effect of prematurity and pro longed labour on the later intelligence of the child Every effort should be made to prevent these two complications

SUMMARY

The possible influence of complications of labour on the cerebral development of pupils at a school for backward children was studied The series consisted of 142 backward-school pupils born in the years 1936 to 1951 whose delivery reports were analysed The results were compared with an equal sized control group consisting of as many girls and boys for each year as the backward-school group, who had completed at least the III grade syllabus of an elementary school The backward-school children included 16 and the elementary school series 2 who weighed under 2,500 g at birth Children weighing over 4,000 g at birth totalled 9 in the backward school series and 17 in the elementary school series Four backward children and 2 elementary school children were delivered by forceps, and the number of breech presentations was 9 and 4, respectively Toxæmia was more frequent in the mothers of the backward children than in those of the elementary school group The duration of labour was significantly ($P = 0.05$) longer in the backward school than in the elementary school group, and cases of labour lasting over 18 and over 24 hours were also statistically ($P = 0.05$) more numerous in the backward school series The incidence of short labour under 6 hours, was equal in the two groups The mothers of the backward school group had had to be given oxytocics or morphine and its derivatives unusually often No distinct differences were established in the mean age of the mothers, the relative number of primiparæ or the mean birth weights The number of unmarried mothers was 11 times greater in the backward school than in the elementary school group This may be indicative of the role of socio economic factors rather than of inferior maternity care

Acknowledgements

We are indebted to Mr H A Alikoski, Mg Phil for the help in the mathematical treatment of the study and to the Sigrid Juselius Foundation for the grant towards the costs of this investigation

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From the Department of Obstetrics and Gynæcology (Professor C A. Gemzell) and the Department of Radiology (Professor F Knutsson) University Hospital Uppsala Sweden

RADIOLOGICAL ESTIMATION OF FŒTAL LENGTH IN THE SECOND TRIMESTER OF PREGNANCY

BY

STIG E J MELANDER BENGT H PERSSON AND STIG FAGERBERG

The fœtal size during the second trimester presents a practical problem in those cases where abortions are to be performed on medico-legal grounds Though the majority of the women give the exact date of their last normal period there are others who for one reason or another cannot give such accurate information Moreover the size of the uterus may give a false impression of the actual size of the fœtus Thus polyhydramnion, multiple pregnancy or soft intramural fibro myomata enlarge the uterus out of proportion to the period of gestation In such cases the necessary information may be obtained by radiological measurements The number of X ray exposures must be restricted in order to reduce maternal and fœtal gonadal irradiation to a minimum This of course means a limit to the radiological procedure used

The common radiological method of estimating the degree of maturity of the fœtus in the latter part of pregnancy is based on skeleton development which follows a relatively constant pattern Measurements of different skull diameters have been used to estimate the size of the fœtus The relationships found between such diameters and fœtal length are based on gross measurements of a large number of formalin fixed fœtuses and still births (Scammon and Calkins 1929)



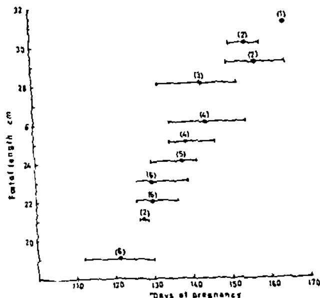


Fig 1 Fœtal length (crown heel) in relation to days of pregnancy as es imated from the first day of the last normal period Figures in brackets denote number of women in each fœtal length-group and the dots represent arithmetical means

tion was examined at intervals of 10° during rotation through its vertical axis from 90° to 0° (*viz* from true lateral to frontal position) An analysis of these films is presented graphically in Fig 2 and illustrated in Fig 3

With our technique the skull of the fœtus is almost invariably presented in a lateral position in one of our 3 films A small deviation of the head from the lateral view cannot of course be ascertained but as will be seen from Fig 2 with a rotation of the skull of up to 20–30° the apparent measurement approximates to the true O F D measurement.

In the majority of the cases the pregnancy was terminated by abdominal transperitoneal Cæsarean section In some cases vaginal Cæsarean section was performed Due to unavoidable damage to the fœtal skull a reliable determination of the O F D by direct measurement was possible in only 24 cases

Few attempts, if any, have been made to correlate the fœtal skull diameters *in vivo*, as measured by radiography, with the length of the fœtus during the second trimester of pregnancy Our intention has been to find out if there exists an approximately constant correlation between the occipito frontal diameter (O F D) of the skull and the fœtal length during the fourth to the sixth month of pregnancy, and if so, if radiological determination of this skull diameter can provide information on the size of the fœtus of such a degree of accuracy that measurements of this type may be of any practical value The primary prerequisite was, however, that the number of X-ray exposures should be sharply limited

Case Material and Methods

Forty-one pregnant women admitted to hospital in the second trimester of pregnancy for legal abortion were studied The material is presented in Fig 1

The radiological investigations were mostly performed the day before operation In no case was there an interval of more than six days between radiological examination and operation

All patients were examined in the prone position using a postero-anterior projection, with a tube distance of 100 cm In the majority of cases one frontal and two oblique views were taken This examination represents a total dose of radiation to the maternal gonads of approximately 0 15–0 20 r, as measured by a ionization chamber inserted in the rectum

The fœtal O F D was measured on the film and corrected for the enlargement By using amniography in some cases we could in lateral views determine the object-film distance to be on the average 15 cm This indicates a correction factor of 0 85

Immediately after the operation the O F D of the fœtus was measured with calipers by one of us (B H P) The fœtus was then stretched out on a table and its crown heel length was measured with the same instrument

The difficulties in obtaining exact lateral projections of the skull *in utero* are obvious and these may lead to geometrical errors In order to determine the correlation between the rotation of the fœtal skull and its projection on the film a skull prepara

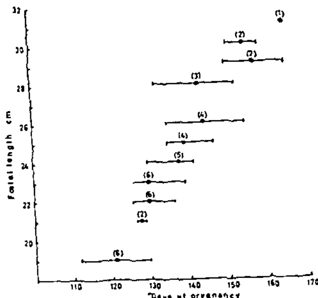


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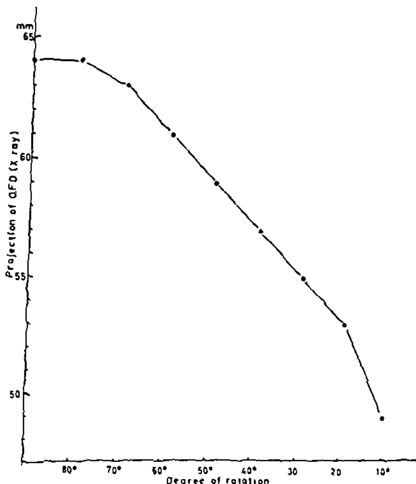


Fig 2 Correlation between rotation of fœtal skull and its projection on the X ray film O F D denotes occipito frontal diameter

Results

The findings are presented in Figs 4 and 5, in which each dot represents one case The regression lines in the diagrams with their equations represent the relation of the average fœtal length to occipito frontal diameter of the fœtal skull In Fig 4 the determinations of the two parametres were made by calipers after operation In Fig 5, on the other hand, the estimation of the O F D, was made by radiography and corrected for the factor of enlargement (0 85), whereas the length of the fœtus was measured after operation by calipers

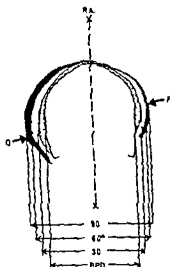


Fig 3 Illustration of the correlation between rotation of fœtal skull and its projection on the X ray film O denotes occiput F frons B P D biparietal diameter and R A rotation axis

It is clearly shown that there is a very high correlation between the increase in fœtal length and O F D in our series It is also clearly shown that there is a difference in the slope of the two regression lines This difference represents the error of the radiological measurements of O F D The average ratio between the radiological and direct measurements of O F D is found to be 0 94 ± 0 01 (M ± S E) This means, that the radiological measurements are in general lower than the direct ones either because of a too low correction factor in certain cases or more probably an indiscernable rotation of the fœtal skull

According to the graph in Fig 2 the average value of 0 94 corresponds to a deviation of the skull to an angle of about 30° Certainly such a small deviation cannot be ascertained by radiography of the fœtal skull *in utero*

The differences between the radiological and direct measurements are reflected in the differences between the average values of the ratios of the fœtal length to O F D as found by the radiological measurement of the skull diameter (4 44 ± 0 05 = M ±

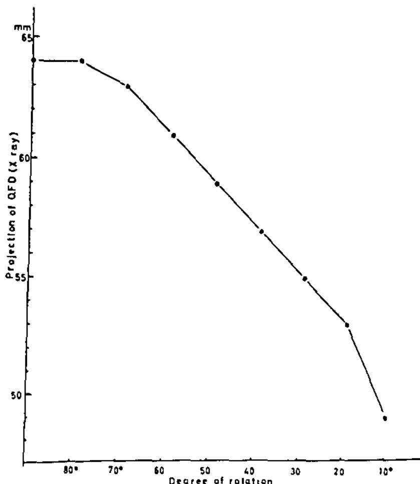


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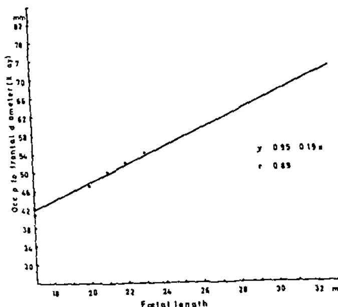


Fig 5 Relationship between fœtal length and occipito-frontal diameter of the fœtal skull measured on the X ray film r = correlation coefficient

In an appreciable number of cases however length of gestation constitutes an uncertain factor In others length of gestation and uterine size disagree In such cases the proposed method of estimating the fœtal length may be a valuable aid in the attempts to deduce the actual stage of pregnancy

As seen in Fig 1 the whole of our material is concentrated in the period between the 16th and 24th weeks and mainly between the 18th and 22nd weeks of pregnancy From the Figure it may be seen that the fœtal length during the 20th week of gestation (133-140 days of pregnancy) may vary between 22 and 28 cm with an average value of 25 cm These figures represent direct measurements on the fœtus immediately after operation The average fœtal length as well as the deviation from this value during the 20th week of gestation correspond to those found by Mall (1910) and Dietrich (1925) The rather great variation in length of the fœtuses at this time of gestation is due to

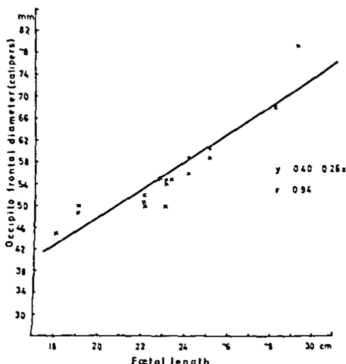


Fig 4 Relationship between fœtal length and occipito frontal diameter of the fœtal skull Measurements by calipers after operation r = correlation coefficient.

S E), and that found by direct measurement (4 13 ± 0 04 = M ± S E) In the individual case multiplication of the radiological estimate of O F D by 4,44 gave an average deviation of the apparent fœtal length from the real value, based on direct measurement, of ± 1,1 cm. ± 0,1 (M ± S E) This average deviation in fact represents the limit of the method when used as described in the present paper

If the method of radiological measurement described in this paper is strictly followed, the crown-heel length of the fœtus may be estimated by multiplication of the O F D in cm, as measured on the X-ray films, with the factor 3 8 This factor includes the enlargement correction

Discussion

According to the Swedish laws certain medico legal abortions must be performed before the end of the 20th week of gestation

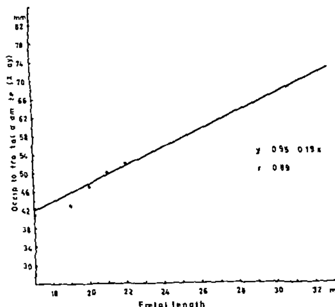


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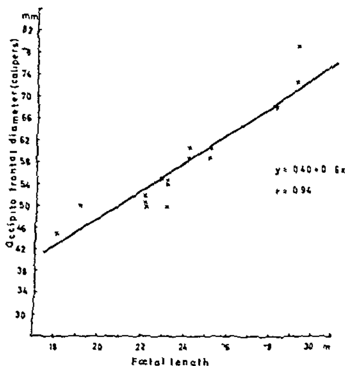


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THE WEIGHT AND LENGTH OF NEWBORN INFANTS IN RELATION TO PARENTAL AGE

BY

J A ABOLINS

Age of Mother

Opinions differ as to a possible connection between the mother s age and the weight and length of the child at birth (Kjolseth, 1913 Perlstein and Lewinson, 1937, Donald, 1939 Millis 1953 Fraccaro 1956 and others) Some of these authors maintain that the weight increases with increasing age of the mother, i e the older the mother the bigger the child (Issmer 1887 Kjolseth 1913, Kontsek 1940 Karn 1952, and others) La Toretta (1955) for example, estimates that for every additional year of maternal age there is an increase of 1 80 g in the weight of boys and 5 04 g in the weight of girls Donald (1939) Mc Keown and Gibson (1951) Fraccaro (1956) among others, are of the opinion, however, that there is no relation between the age of the mother and the weight and length of the child at birth

Many authors speak of an optimal child bearing age Gerschenson (1931) considers it to be the age between 25 and 35 years Bode (1936) the age between 16 and 25 years Strempel (1936) the age between 25 and 29 years Kontsek (1940) the age of 28 years Cullumbine (1950) the age between 26 and 30 years Mukherjee and Biswas (1959) the age between 25 and 30 years De La Fuente and Gracian (1956) state that *very young and very old* mothers bear small children

either biological variations of fœtal growth or to our ignorance of the exact day of conception This last mentioned factor must indeed be an important one with regard to the high speed of growth of the fœtus especially during the 4th and 5th month of gestation As estimated by Mall (1910) and Gengenbach (1932) the length of the fœtus increases by approximately 3 mm every day during the 16th to the 20th week Therefore, at this period of fœtal development a deviation of one week in the estimated date of conception results in a variation in fœtal length of about 2 cm

SUMMARY

A radiological method of estimation of fœtal length during the second trimester of pregnancy is presented The correlation between the occipito frontal diameter and the crown heel length of the fœtus has been studied in 41 cases during the 16th to the 24th week of gestation By the use of a standardized radiological technique it is possible with a very low dose of radiation to determine the fœtal length during the time mentioned with reasonable accuracy

Clinical as well as medico legal aspects of the value of the method are discussed

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Table III *Weight of Newborn Infants (Boys only) in Relation to Maternal Age and Parity in Karn and Penrose's Series*

	Birth Weight (lbs)					
Age	I paræ	II paræ	III paræ	IV V paræ	VI VII-paræ	VIII paræ
—20	7 24	7 61	7 99			
+20	7 14	7 46		7 60	7 39	
+24	7 21	7 38	7 71			
+28	7 15	7 37	7 69	7 58	8 08	8 18
+32	7 06	7 36	7 39	7 51	7 82	8 85
+36	7 09	7 19	7.49	7 61	7 80	8 96
40—	6 90	7 16	7 99	7 91	7 49	8 02

Karn and Penrose conclude that the birth weight decreases slightly with increasing maternal age

Table IV *Weight of Newborn Infants (Boys only) in Relation to Maternal Age (Primiparæ only)*

Age	M	σ	V	No
	Boys (Mothers married)			
	Birth Weight (g.)			
−20	3 514 ± 42 2	406 ± 29 8	11 7 ± 0 8	93
21–25	3 519 15 8	418 11 2	11 8 0 3	697
26–30	3 538 15 1	424 10 7	11 9 0 3	787
31–40	3 513 17 6	414 12.4	11 8 0 4	557
41–	3 438 88 5	451 62 6	13 3 1 8	26
	Girls (Mothers married)			
−20	3 385 ± 44 9	432 ± 31 7	12 8 ± 0 9	90
21–25	3 393 12 3	424 11 3	12 5 0 3	701
26–30	3 430 14 6	410 10 6	12 0 0 3	783
31–40	3 373 17 3	408 12 3	12 1 0 4	552
41–	3 197 91 5	466 64 7	14 6 2 0	32

* M (*Median*) $= \frac{\Sigma X}{n}$ σ (*Standard Deviation*) $= \pm\sqrt{\frac{\Sigma (X-M)^2}{n}}$ V (Coefficient of Variation) $= \frac{100\,\sigma}{M}$

Karn and Penrose (1951), among others, maintain that the birth-weight decreases with increasing age of the mother

Some data from the literature are given in Tables I and II

Table I *Data from the Literature on the Weight and Length of New born Infants in Relation to Maternal Age*

Pettersson (1882)		Kjølseth (1913)		
Age	Weight at Birth g	Age	Weight at Birth g	Length at Birth cm.
15–19	3 451	–20	3 455	50 61
20–24	3 485	21–24	3,453	50 81
25–29	3,591	25–29	3 524	50 98
30–34	4,062	30–34	3 556	51 92
35–39	3,595	35–39	3,630	51 51
40–44	3,676	40–44	3,645	51 29
		45–49	3,694	52 00

Table II *Data from the Literature on the Weight and Sex of New born Infants in Relation to Maternal Age and Duration of Pregnancy*

	Karn and Penrose (1951)			
	Boys		Girls	
Age	Weight at Birth (lbs)	Duration of Gestation (days)	Weight at Birth (lbs)	Duration of Gestation (days)
—20	7.259	279 78	7 041	281 39
+20	7 303	281 23	7 033	282 58
+24	7 327	281 18	7 140	281 93
+28	7 368	281 41	7 145	281 29
+32	7 358	279 30	7 201	280 56
+36	7 480	279 21	7 249	280 21
40—	7 566	278 59	7 252	277 66

These figures show an increase in weight in relation to the increasing age of the mothers When, however, the series is divided into groups according to maternal age and the number of deliveries, the figures of birth-weight are as shown in Table III (only data referring to boys are included)

ge	M		σ		V		No	Sex of Child	Civil S of Mo
20	52 05 ±	0 36	2 01 ±	0 26	3 35 ±	0 49	31		
25	51 73	0 30	2 06	0 21	3 97	0 49	47		
30	52 01	0 32	2 22	0 23	4 28	0 43	49	Boy	Unma
-35	52 81	0 42	2 09	0 30	3 95	0 56	25		
)	52 33	0 53	1 84	0 38	3 52	0 72	12		
-	52 00	1 14	2 27	0 80	4 37	1 55	4		
-20	3 421 ±	31 9	405 7	± 22 6	11 9	± 0 66	162		
5	3 432	9 6	407 9	6 8	11 9	0 20	1 806		
)	3 415	7 9	407 9	5 6	12 0	0 16	2 650	Girl	Mar
-35	3 399	11 7	426 8	8 3	12 6	0 24	1 322		
	3 353	19 7	426 1	13 9	12 7	0 41	468		
	3 263	43 7	396 1	30 9	12 1	0 95	82		
-20	3 263 ±	33 5	437 2	± 23 7	13 4	± 0 73	170		
1 25	3 319	20 7	386 3	12 6	11 6	0 44	349		
-30	3 288	25 8	389 0	18 2	11 8	0 56	228	Girl	Unm
31-35	3 255	40 7	372 9	28 8	11 5	0 89	84		
	3 254	57 0	370 5	40 3	11 4	1 25	42		
-	3 325	105 0	297 6	74 5	8 9	2 24	8		
-20	3 510 ±	36 0	484 3	± 25 4	13 8	± 0 77	181		
	3 556	31 4	431 3	22 2	12 1	0 62	1 893		
	3 530	8 4	440 8	5 9	12 5	0 17	2 772	Boy	Ma
1-35	3 503	12 2	440 5	8 6	12 6	0 78	1 317		
40	3 456	21 2	445 6	14 9	12 9	0 43	448		
	3 441	57 8	469 0	40 8	13 6	1 19	66		
-20	3 436 ±	30 2	392 9	± 21 4	11 5	± 0 62	170		
-25	3 420	22 0	427 5	15 5	12 5	0 45	379		
)	3 411	26 0	422 3	18 4	12 4	0 54	264	Boy	Unr
)	3 456	42 7	418 7	30 2	12 1	0 88	96		
	3 539	42 8	548 9	58 5	15 5	1 65	44		
1-	3 571	130 4	487 1	92 0	13 7	2 58	14		

series that I now subscribe to the opinion of Lundh (1926) Martin (1931) Lenner (1943), Klein (1946) Mc Keown and Gibson (1951) Millis and Seng (1954) Khalap (1956) and others who consider that the age of the mother has practically no influence on the child s birth weight and length

Venge (1948) arrived at a similar conclusion in his investigations on cattle However, Bluhm (1929), in his animal studies did not discover any influence of the age factor on the birth weight

In an investigation of primiparæ (1938) I obtained the result shown in Table IV

The figures indicate a certain increase in the birth weight up to the age of 30 I therefore joined in supporting the theory of an optimal age for child-bearing

Recently, an investigation of a series of cases seen at the Maternity Home Pro Patria and the Allmanna Barnbordshuset respectively, has been carried out which comprised 83,677 primiparæ The results are shown in Tables V and VI

The differences in birth weight and length of the newborn in relation to the age of the mothers are so slight in the present

Table V *Weight of Newborn Infants in Relation to the Age and Civil Status of the Mother in the Pro Patria Series*

Age	M	σ	V	No	Sex of Child	Civ of
-20	50 42 ± 0 22	2 12 ± 0 16	4 12 ± 0 31	91		
-25	51 39 0 07	2 16 0 05	4 21 0 09	1 115		
-30	51 59 0 05	2 12 0 04	4 11 0 07	1 784	Girl	Ma
-35	51 61 0 01	2 18 0 05	4 21 0 10	885		
-40	51 56 0 13	2 18 0 09	4 21 0 17	300		
-	51 19 0 36	2 34 0 25	4 55 0 50	42		
-20	50 12 ± 0 36	1 78 ± 0 26	3 54 ± 0 61	24		
-25	50 69 0 27	1 77 0 19	3 49 0 38	43		
-30	50 95 0 36	2 03 0 26	3 98 0 51	31	Girl	Unm
-35	50 79 0 43	1 60 0 30	3 14 0 59	14		
-40	50 73 0 52	1 86 0 36	3 66 0 72	13		
-	52 75 0 39	0 39 0 28	1 47 0 52	4		
-20	51 76 ± 0 23	2 31 ± 0 11	4 45 ± 0 32	98		
-25	52 15 0 06	2 00 0 04	4 01 0 08	1 175		
-30	52 28 0 05	2 22 0 04	4 24 0 07	1 883	Boy	Marr
-35	52 17 0 08	2 25 0 05	4 31 0 10	911		
-40	52 17 0 13	2 18 0 09	4 19 0 17	201		
[illegible]	[illegible]	2 10 0 24	4 18 0 46	42		

M	σ	V	No	Sex of Child
3 483 ± 10 5	453 3 ± 7.4	13 0 ± 0 21	Same as above	Boy
3 483 5 0	436 9 3 6	12 6 0 10		
3 485 5 5	441 2 3 9	12 7 0 11		
3 485 8 5	452 5 6 0	13 0 0 17		
3 461 14 4	449 3 10 2	13 0 0 29		
3 4-8 32 7	443 3 23 1	12 9 0 68		
3 375 ± 6 4	432 6 ± 4.5	12 8 ± 0 13	Same as above	Boy
3 363 5 0	428 5 3 6	12 8 0 11		
3 343 8 2	428 1 5 8	12 8 0 17		
3 351 14 6	442 9 10 3	13 2 0 31		
3 300 24 6	427 8 17.4	13 0 0 53		
3 219 63 2	442 3 44 7	13 8 1 39		

Table VII *Weight of Newborn Infants in Relation to the Age of the Father According to Cullumbine (1950)*

Age of Father	Primiparæ Birth Weight (lbs)	Total No Birth Weight (lbs)
19–20	5 68	5 68
21–25	5 79	5 82
26–30	5 84	6 02
31–35	5 98	6 26
36–40	5 78	6 31
41–50	5 80	6 32
51–	–	5 80

Age of Father and Difference in Age of the Parents

To my knowledge the medical literature only comprises a small number of papers dealing with the influence of the father s age on the birth weight and length of the child e g those of Kontsek (1940), Cullumbine (1950), and Halevi Bromberg and Brzezinsky (1951) Some figures taken from Cullumbine s report are given in Table VII

The above data show an increase in birth weight up to the time when the father is 50 years of age From the results of two investigations Kontsek states the age for maximum weight of

Table VI *Weight of Newborn Infants in Relation to the Age and Civil Status of the Mother in the Allmänna Barnbördshuset Series*

Age	M	σ	V	No.	Sex of Child	Civil St of Mot
-20	50 51 ± 0 05	1 92 ± 0 04	3 79 ± 0 06	1,763		
21-25	50 62 0 02	1 89 0 02	3 66 0 03	6,962		
26-30	50 50 0 03	1 90 0 02	3 74 0 03	5,767	Girl	Marri
31-35	50 84 0 04	1 94 0 03	3 82 0 05	2,702		
36-40	50 79 0 06	2 01 0 05	3 96 0 09	1,004		
41-	50 48 0 31	1 84 0 09	3 65 0 19	190		
-20	50 45 ± 0 03	2 02 ± 0 02	3 98 ± 0 04	4,064		
21-25	50 26 0 03	2 12 0 02	4 21 0 04	6,757		
26-30	50 13 0 04	2 08 0 03	4 15 0 06	2 669	Girl	Unmarr
31-35	50 27 0 08	2 18 0 06	4 35 0 11	738		
36-40	50 06 0 14	2 24 0 10	4 48 0 20	263		
41-	50 30 0 30	2 10 0 21	4 00 0 47	46		
-20	51 26 ± 0 05	2 06 ± 0 03	4 02 ± 0 07	1,863		
21-25	51 40 0 02	2 02 0 03	3 92 0 03	7,600		
26-30	51 51 0 03	2 08 0 02	4 03 0 04	6 499	Boy	Marrie
31-35	51 58 0 04	2 08 0 05	4 02 0 05	2 812		
36-40	51 57 0 07	2 22 0 05	4 31 0 10	976		
41-	51 35 0 16	2 17 0 11	4 23 0 22	183		
-20	51 04 ± 0 03	2 15 ± 0 02	4 20 ± 0 04	4,542		
21-25	50 89 0 03	2 27 0 02	4 45 0 04	7 241		
26-30	50 79 0 04	2 30 0 03	4 52 0 06	2 749	Boy	Unmarr
31-35	50 96 0 08	2 30 0 05	4 51 0 11	924		
36-40	51 05 0 14	2 44 0 10	4 77 0 20	303		
41-	50 87 0 35	2 47 0 25	4 88 0 49	49		
-20	3,358 ± 10 0	418 8 ± 7 0	12 5 ± 0 21			
21-25	3,358 4 9	405 9 3 4	12 1 0 10			
26-30	3,367 5 5	414 1 3 9	12 3 0 11	Same as above	Girl	Married
31-35	3,381 8 0	416 0 5 7	12 3 0 17			
36-40	3,330 14 0	444 5 9 9	13 4 0 30			
41-	3,233 29 2	401 0 20 6	12 5 0 64			
-20	3,285 ± 6 3	403 9 ± 4 5	12 3 ± 0 14			
21-25	3,262 4 9	399 1 3 4	12 2 0 11			
26-30	3,246 7 7	397 6 5 4	12 3 0 17	Same as above	Girl	Unmarri
31-35	3,232 14 6	395 5 10 3	12 2 0 32			
36-40	3,224 26 6	428 4 18 7	13 3 0 58			
41-	3,252 60 0	406 7 42 5	12 5 1 30			

M	σ	V	No	Sex of Child	Civi of
3 483 ± 10 5	453 3 ± 7 4	13 0 ± 0 21			
3 483 5 0	436 9 3 6	12 6 0 10	Same as above	Boy	M
3 485 5 5	441 2 3 9	12 7 0 11			
3 485 8 5	452 5 6 0	13 0 0 17			
3 461 14 4	449 3 10 2	13 0 0 29			
3 478 32 7	443 3 23 1	12 9 0 68			
3 375 ± 6 4	432 6 ± 4 5	12 8 ± 0 13			
3 363 5 0	428 5 3 6	12 8 0 11	Same as above	Boy	Un
3 343 8 2	428 1 5 8	12 8 0 17			
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26–30	5 84	6 02
31–35	5 98	6 26
36–40	5 78	6 31
41–50	5 80	6 32
51–	–	5 80

Age of Father and Difference in Age of the Parents

To my knowledge the medical literature only comprises a small number of papers dealing with the influence of the father s age on the birth weight and length of the child, e g those of Kontsek (1940) Cullumbine (1950), and Halevi Bromberg and Brzezinsky (1951) Some figures taken from *Cullumbine s* report are given in Table VII

The above data show an increase in birth weight up to the time when the father is 50 years of age From the results of two investigations Kontsek states the age for maximum weight of

the child as the father's 44th and 48th year respectively The two investigations give no information on the difference in age of the parents and its influence on the birth weight of the child

Halevi *et al* (1951) observed that children born to mothers older than their husbands were smaller, and found that the birth weight decreased with increased difference in parental age Their results were not, however, absolutely statistically significant

My observations are similar but in a study of the age difference between the parents and the birth weight of the child I obtained the results shown in Table VIII which refer to boys only (mothers primiparæ, parents married)

Table VIII *Weight of Newborn Infants in Relation to the Age Difference between the Parents (Boys Only, Mothers Primiparæ, Parents Married)*

	Birth Weight (g.)						
	M		σ		V		No.
Father Older							
1– 5 years	3 471 ±	14 9	440 ±	10 5	12 7 ±	0 3	202
6–10	3 520	21 1	420	15 0	12 0	0 4	297
11–	3 493	30 4	432	21 5	12 4	0 6	887
Parents of the Same Age	3,513	28 6	401	20 2	11 4	0 6	197
Mother Older							
1– 5 years	3 453	22 6	450	16 0	13 0	0 5	296
6–10	3 447	58 1	510	41 1	14 8	1 2	77
11–	3 607	210 9	558	144 2	15 5	4 1	7

Neither in relation to the age of the father nor to the difference in the age of the parents were there any statistically significant differences in birth weight As I have not been able to prove that the maternal age has an influence on the birth weight of the child it would hardly seem likely that the age of the father should be of any importance in this connection nor the difference in the age of the parents

SUMMARY

Opinions are divided as to the influence of the parental age and age difference between the parents on the weight and length of the child at birth

An investigation of 83,677 first born at the Pro Patria Maternity Home and the Allmänna Barnbordshuset, Stockholm, Sweden, has shown that the parents' age and difference in age have practically no influence on the child s weight and length at birth

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Table VIII *Weight of New born Infants in Relation to the Age Difference between the Parents (Boys Only, Mothers Primiparæ, Parents Married)*

	Birth Weight (g)						
	M		σ		V		No
Father Older							
1– 5 years	3,471 ±	14.9	440 ±	10.5	12.7 ±	0.3	202
6–10	3,520	21.1	420	15.0	12.0	0.4	397
11–	3,493	30.4	432	21.5	12.4	0.6	857
Parents of the Same Age	3,513	28.6	401	20.2	11.4	0.6	197
Mother Older							
1– 5 years	3,453	22.6	450	16.0	13.0	0.5	396
6–10	3,447	58.1	510	41.1	14.8	1.2	77
11–	3,607	210.9	548	144.2	15.5	4.1	7

Neither in relation to the age of the father nor to the difference in the age of the parents were there any statistically significant differences in birth weight As I have not been able to prove that the maternal age has an influence on the birth weight of the child it would hardly seem likely that the age of the father should be of any importance in this connection nor the difference in the age of the parents

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THE FREQUENCY OF CONTRACTIONS DURING NORMAL LABOUR

BY

LENNART LINDGREN

The frequency and strength of contractions are the most important factors in a clinical estimation of the intensity of labour The effect of labour, however, is determined by the degree of cervical dilatation and the position of the presenting part of the fœtus By uterine activity is meant the product of the intensity (amniotic pressure minus amniotic tone) and the frequency of contractions The uterine activity is usually expressed in Montevideo-units (M U), i e the product of intensity and frequency of contractions for 10 minutes Good progress in labour is associated with a high frequency of contractions whereas a low frequency is found with hypotonic inertia A high frequency, however, occurs often with hypertonic inertia as uterine fibrillation

In most textbooks (Williams, 1956, Baird, 1957, Martius, 1959, Greenhill, 1960, and others) it is reported that the frequency of contractions is low in the beginning of labour (one contraction every 10th to 30th minute) and successively increases to one contraction every 2nd to 3rd minute at delivery Westermark (1893) arrived at the same results by using intra-uterine tocography In distinction to this Schäffer (1896) found about the same frequency during the whole labour – about one contraction every 3rd minute In an investigation with intra-uterine tocography (Lindgren, 1959) has been observed

that the frequency of contractions increases after rupture of mem branes and is higher in multiparæ

The object of this investigation was to study the frequency of contractions under different conditions and to show the effect of variation on normal labour

Method and the Series

The method of intra uterine tocography developed by Ingel man Sundberg and Lindgren (1955) was adopted The frequency of contractions was estimated together with the amniotic pressure and the tone (a) at the initial stage of labour (b) at every centimeter of cervical dilatation (c) during descent of the fœtal head and (d) from the time the fœtal head reached the pelvic floor until delivery As the onset of labour cannot be exactly determined the whole initial stage was not registered the recordings being in all cases made from about ten minutes to four hours prior to the effacement of the cervix

The series consisted of 100 patients who were admitted to hos pital in labour The cervix was not taken up on admission All the patients had *occipito anterior vertex* deliveries None showed signs of incoordinated contractions or disproportion Dispropor tion was excluded in doubtful cases by X ray

There were 75 primigravidæ and 25 multiparæ Twenty pa tients were II paræ four III paræ and one was a IV para The age of the primigravidæ varied from 17 to 42 years and that of the multiparæ from 21 to 43 years with a mean age of 25 5 + 0 6 and 28 1 ± 1 1 years respectively

The birth weight of the children of the primiparæ ranged from 2 440 to 4 290 g and that of the multiparæ from 2 860 to 5 120 g and was on an average 3 460 ± 37 and 3 770 ± 100 g res pectively The corresponding values for the circumference of the fœtal head were 31 and 37 cm 32 and 37 cm 33 6 ± 0 2 and 34 6 + 0 2 cm respectively

During the first stage of labour 39 primigravidæ had unruptured membranes in 14 the membranes ruptured during the recording and in 22 the membranes had ruptured before the registration The duration of the first stage from the time the cervix was

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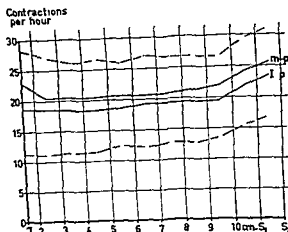


Fig 1 Frequency of contractions

I initial stage 2–10 cm degree of cervical dilatation S_1 the first part of the second stage S_2 the second part of the second stage I p primigravidæ m p multiparæ The broken lines showed 95 per cent confidence interval

Table I *Contractions per Hour*

	Primiparæ	Multiparæ	Schaffer
Initial stage	18.8 ± 0 8	23 0 ± 2 2	
First stage Part I (cx 2–6 cm.)	18 6 ± 0 4	20 5 ± 0 8	20 1
First stage Part II (cx 6–10 cm.)	19 6 ± 0 4	21.2 ± 0 6	18 5
Second stage Part I	21 9 ± 0 8	24 2 ± 1 1	19.8
Second stage Part II	23 5 ± 0 8	25.8 ± 1.4	21.4

cx = cervix

before the initial recording is less than for the whole series, but is still statistically significant In primigravidæ the difference was 3 3 ± 1 0 and in multiparæ 3 5 ± 1 1 contractions per hour ($P < 0\ 001$)

The series was divided into three groups according to the frequency of contractions during the initial stage The initial frequency was less than 16 contractions per hour in 33 patients (6

taken up until it was fully dilated was for the three groups of patients 10 6 ± 0 8, 7 8 ± 1 2, and 7 4 ± 1 1 hours respectively

Fifteen multiparæ had unruptured membranes, in 4 they ruptured during the recording, and 6 had ruptured membranes before the recording The duration of the first stage for these groups of multiparæ was 4 3 ± 0 5, 3 2 ± 0 5, and 3 0 ± 0 5 hours, respectively

The second stage of labour lasted 1 64 ± 0 11 hour in the primigravidæ and 0 65 ± 0 11 hour in the multiparæ The first part of the second stage (*i e* from the time of full dilatation of the cervix until the fœtal head reached the pelvic floor) took 0 79 ± 0 07 hours for primigravidæ and 0 33 ± 0 07 hours for multipara. The corresponding time for the second part of the second stage (*i e* until delivery) was 0 85 ± 0 07 and 0 32 ± 0 05 hours, respectively

All patients were delivered within 24 hours from the time the cervix was taken up

Comparison between mean values has been based on *Student's* t-test

The Frequency of Contractions during the Different Stages of Labour

The frequency of contractions in primigravidæ and multiparæ was about the same during the initial stage and during cervical dilatation (Fig 1), but during the second stage of labour the frequency increased in both groups In Table I are given the mean values for frequency during the initial stage, the first part of cervical dilatation (up to 6 cm), the second part of cervical dilatation, the first part of the second stage (until the fœtal head has reached the pelvic floor) and for the rest of the second stage of labour The primigravidæ as well as the multiparæ showed a higher frequency of contractions during the second stage in comparison with the first stage, or 3 5 ± 0 6 and 4 1 ± 1 0 contractions per hour higher frequency respectively ($P < 0\ 001$) This increase of frequency is partly due to the effect of the rupture of membranes (Fig 2) The difference between the frequency in the first and second stages in patients with ruptured membranes

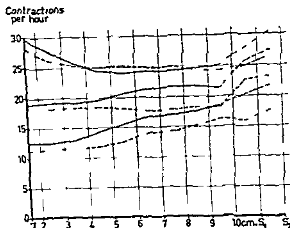


Fig 3 Frequency of contractions
Indications as in Figs 1 and 2.

the initial stage ($P < 0.001$)[1] The second part of the first stage showed an insignificant increase of the amniotic pressure in comparison with the first part or 2.1 ± 1.1 mm Hg ($P < 0.05$) During the second stage of labour the amniotic pressure substantially increased by contractions of the corpus only The values however are somewhat unreliable as some of the patients did not relax between the bearing down contractions The increase of the amniotic pressure during the first part of the second stage in comparison with the second part of the first stage was $13.0 + 3.0$ mm Hg ($P < 0.001$) The corresponding increase of the amniotic pressure during the second part of the second stage in comparison with the first part was 10.7 ± 4.0 mm Hg ($0.01 > P > 0.001$) The maximum increase of the amniotic pressure during the bearing down contractions was during the first and second parts of the second stage 104.7 ± 4.1 and 121 ± 5.2 mm Hg respectively

The frequency of contractions during every phase of labour as plotted in Fig 1 has been correlated to the corresponding

[1] The amniotic pressure was measured on 52 patients 35 of which were primiparæ

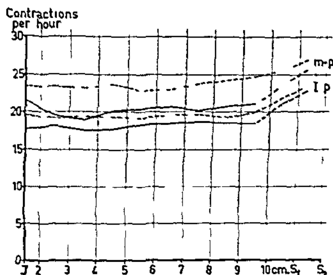


Fig 2 Frequency of contractions
Before (————) and after (- - - - - - - -) rupture of membranes
Indications as in Fig 1

multiparæ), 16 to 24 contractions per hour in 40 patients (10 multiparæ), and more than 24 contractions per hour in 27 patients (9 multiparæ) In the group with a low initial frequency the frequency increased during the whole labour (Fig 3) The middle group showed unchanged frequency during the first stage, but in the group with a high initial frequency, the frequency decreased during cervical dilatation In both latter groups the frequency also increased during the second stage In the group with a low initial frequency the difference between the first and second parts of cervical dilatation was 3 5 ± 0 7 contractions per hour ($P < 0\ 001$) The corresponding difference in the other groups was 1 1 ± 0 8 ($P > 0\ 15$), and 2 1 ± 0 8 ($0\ 01 > P > 0\ 001$) contractions per hour respectively

The Frequency of Contractions and the Amniotic Pressure

The amniotic pressure is increased during labour, as is shown in Fig 4 where the series is divided according to rupture of membranes and parity During the first part of cervical dilatation the amniotic pressure was 6 9 ± 1 7 mm Hg higher than during

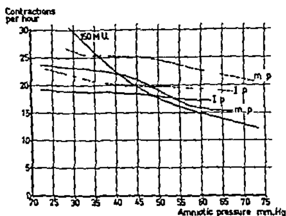


Fig 5 Frequency of contractions and amniotic pressure
Initial and first stage The curve of 150 MU uterine activity is plotted Indications as in Fig 1

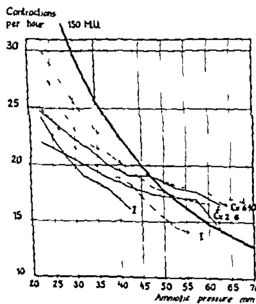


Fig 6 Frequency of contractions and amniotic pressure
Primigravidæ I initial stage Cx 2–6 first part of first stage Cx 6–10 second part of first stage

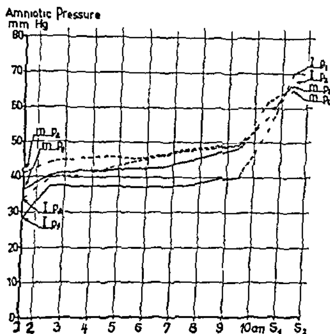


Fig 4 Amniotic pressure

I p_1, primigravidæ with unruptured membranes I p_2, primigravidæ with *ruptured membranes* m p_1, multiparæ with unruptured membranes m p_2 multiparæ with ruptured membranes Other indications as in Figs 1 and 2

amniotic pressure (Fig 5) Because of the unreliable value of the amniotic pressure caused by the corpus contractions during the second stage of labour, only values obtained during the initial recording and the first stage were included The frequency of contractions decreased with increased amniotic pressure in all groups, if the series is divided according to rupture of membranes and parity In the whole series the frequency decrease was 2 6 ± 0 8 contractions per hour at an amniotic pressure of more than 45 mm *Hg* in comparison with an amniotic pressure of or less than 45 mm *Hg* (*P* = 0 001) Fig 5 shows that the frequency decreased more at increased amniotic pressure, if uterine activity was constant The curve of 150 M U is plotted on the figure If the series of recordings is divided into initial and first and second parts of the first stage of labour, the frequency is found to decrease more at increased amniotic pressure and the correlation curves correspond better to the curve of unchanged

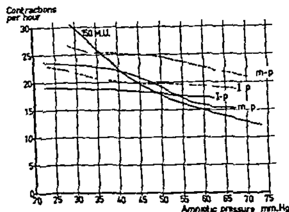


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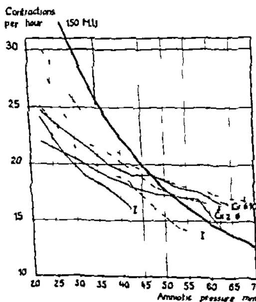


Fig 6 Frequency of contractions and amniotic pressure
Primigravidæ I initial stage Cx 2–6 first part of first stage Cx 6–10 second part of first stage

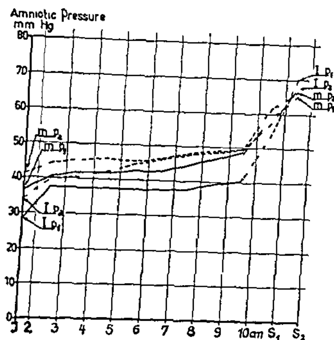


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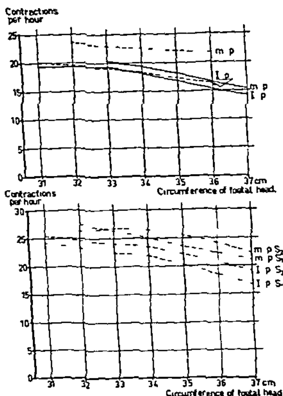


Fig 9 Frequency of contractions and sizes of fœtus
Upper diagram the first stage Lower diagram the second stage
Indications as in Fig 1

uterine activity (Figs 6 and 7) This corresponds with the results of Caldeyro Barcia *et al* (1957) The difference in the frequencies is due to the fact that uterine activity increases during labour

The frequency of contractions was greater with higher amniotic tone (Fig 8) The series was divided into two groups with an amniotic tone of up to and more than 10 mm Hg In the group with higher amniotic tone the frequency was 2 8 ± 0 7 contractions per hour greater than in the group with lower amniotic tone ($P < 0.001$)

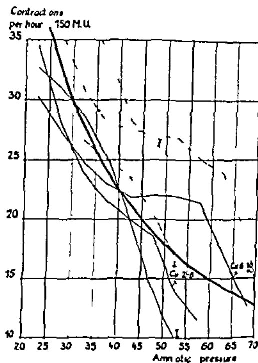


Fig 7 Frequency of contractions and amniotic pressure Multiparae Indications as in Fig 6

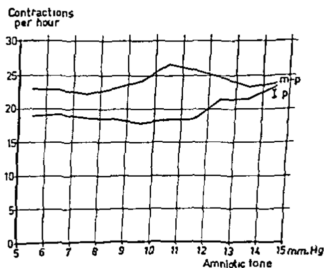
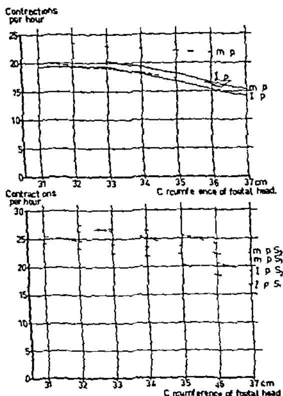


Fig 8 Frequency of contractions and amniotic tone Indications as in Fig 1



F g 9 Frequency of contractions and sizes of fœtus
Upper diagram the f rst stage Lower diagram the second stage
Ind cations as n F g 1

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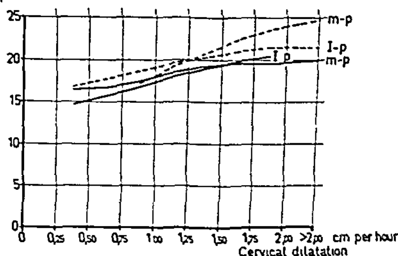


Fig 10 Frequency of contractions and rate of cervical dilatation
Indications as in Fig 1

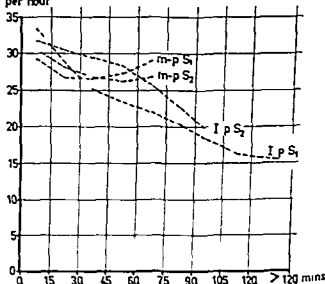


Fig 11 Frequency of contractions and duration of second stage

I pS1, primigravidæ during first part of second stage I pS primigravidæ during second part of second stage m pS1 multiparæ during first part of second stage m pS multiparæ during second part of second stage

The Frequency of Contractions in Relation to Size of Fœtus

The mean frequency of contractions diminished the larger the fœtus (i e the larger the occipito-bregmatic fœtal head circumference) both during the first and second stages of labour (Fig 9) Thus, with a fœtal head of up to 34 cm. circumference the frequency was 2 8 ± 1 0 contractions per hour greater (0 01 > P > 0 001) than with a fœtal head circumference larger than 34 cm The corresponding figures for the second stage of labour were 3 5 ± 0 8 contractions per hour (P < 0 001)

The Frequency of Contractions and the Duration of Labour

The frequency of contractions has been correlated to the duration of the first stage of labour from the time the cervix was taken up As in some cases the membranes ruptured during the recording the duration of the first stage has been expressed as the rate of cervical dilatation in centimeters per hour In all groups, if the series is divided according to rupture of membranes and parity the frequency of contractions increases with more rapid cervical dilatation (Fig 10) The frequency in patients with a rate less than 1 25 cm per hour (i e the duration of the first stage was more than 6 hours) was 3 7 ± 0 6 contractions per hour less than in patients with a rate of cervical dilatation of more than 1 25 cm per hour (P < 0 001)

The frequency of contractions decreased in primigravidæ when the duration of the second stage was longer but not in *multiparæ* (fig 11) Patients with a second stage of up to 2 hours showed

Table II *Length of the First and Second Stages of Labour Contractions per Hour during Initial Stage*

	< 16	16 – 24	> 24
First stage l p	13 6 ± 2 5 hour	6 6 ± 0 7 hour	9 3 ± 2 3 hour
First stage m p	7 6 ± 4 6	2 6 ± 1 2	3 6 ± 1 8
Second stage l-p	1 8 ± 0 2	1.4 ± 0 2	1 6 ± 0 3
Second stage m p	0 7 ± 0 2	0 6 ± 0 1	0.7 ± 0 2

l p primiparæ m p multiparæ

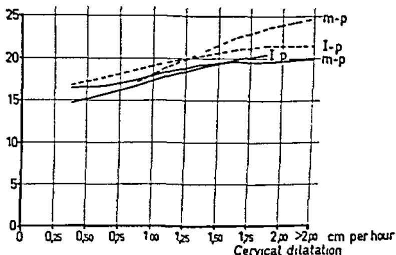


Fig 10 Frequency of contractions and rate of cervical dilatation Indications as in Fig 1

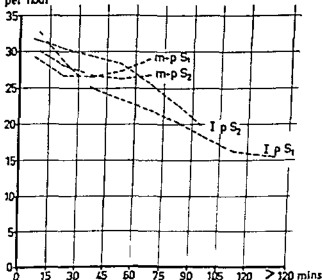


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I pS_1, primigravidæ during first part of second stage I pS, primigravidæ during second part of second stage m pS_1 multiparæ during first part of second stage m pS multiparæ during second part of second stage

during both the first and the second stages and with due regard to rupture of membranes and parity This circumstance together with the increased tissue resistance (Lindgren, 1961) seems to explain why labour takes longer with larger babies in spite of stronger contractions

With increasing frequency the duration of both the first and second stages of labour increases which corresponds to clinical experience A low initial frequency is followed by a longer duration of first and second stages than in a high average initial frequency The duration of labour is rather longer after a high initial frequency than after an average initial frequency but this difference is statistically not significant

SUMMARY

In order to obtain some information on the frequency of contractions during labour the contractions were recorded by intra uterine tocography from the initial stage of labour until delivery

The series consisted of 100 patients 75 of which were primiparæ and 25 multiparæ

The frequency of contractions was in most cases uniform (about one contraction every 3rd minute) during the initial stage of labour and during dilatation of the cervix During the second stage the frequency increased to two contractions every 5th minute If the initial frequency was low the frequency increased throughout labour If the initial frequency was higher a decrease occurred but with an average initial frequency (one contraction every 3rd minute) the frequency only increased during the second stage of labour With increasing amniotic pressure the frequency decreased but not so much as corresponding to unchanged uterine activity A high amniotic tone was followed by a high frequency Patients with a small fœtus had a higher contraction frequency than patients with a large one Rapid labour occurred in association with a high contraction A low initial frequency was followed by a longer duration of labour than a high or average initial frequency It was also found however that labour tended to be prolonged if the initial contraction frequency was higher than if the initial contraction frequency was average

a frequency of 6 3 ± 1 6 contractions per hour higher than the patients whose second stage was more than 2 hours (P < 0 001)

The duration of the first and second stages for primigravidæ and multiparæ was shortest in patients with an initial frequency of 16–24 contractions per hour (Table II) Patients with a low initial frequency had slower labours in all groups A high initial frequency was followed by shorter labour but not so short as in the group with about one contraction every 3rd minute

Discussion

The investigation has shown that the frequency of contractions on an average is about one contraction every 3rd minute during the initial stage and during cervical dilatation This corresponds with the results of Schaffer (1896) and is also found if the series is divided according to rupture of the membranes and parity Contrary to the observations of Schaffer who reported that there was no difference between the first and second stages of labour in respect to the frequency of contractions it was found that the frequency increased during the second stage A low frequency during the initial stage gradually increased during the whole labour A high initial frequency decreased and an initial frequency of about one contraction every 3rd minute was unchanged during cervical dilatation but increased during the second stage These observations explain why Westermark (1893) found a steady increase of the frequency during the whole labour In our series we also noted that the amniotic pressure and the strength of contraction increased during the whole labour This increase of pressure was greatest when cervical dilatation commenced The increase of amniotic pressure may explain the clinical observation that the frequency of contractions gradually increases during labour probably because weak contractions do not cause any pain

The intensity of labour is estimated according to the frequency of contractions, the amniotic pressure, and the amniotic tone At increased amniotic pressure the frequency decreases Increasing frequency is followed by an increase in amniotic tone

With greater fœtal size the frequency of contractions decreases

during both the first and the second stages and with due regard to rupture of membranes and parity This circumstance together with the increased tissue resistance (Lindgren, 1961) seems to explain why labour takes longer with larger babies in spite of stronger contractions

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From the Department of Obstetrics and Gynæcology II (Professor P Bergman), Sahlgrenska Sjukhuset Goteborg, Sweden

THE VALUE OF THE VACUUM EXTRACTOR AS JUDGED FROM USE IN ELDERLY PRIMIPARÆ

BY

P BERGMAN T MALMSTRÖM, and I-M. SCHÖÖN

In a previous paper (Bergman and Malmstrom, 1961) the perinatal mortality in a series in which delivery was completed with the vacuum extractor (VE), was compared with a series in which forceps was used In that investigation the cases had been collected in 1958 from twenty nine departments of gynæcology and obstetrics in Swedish hospitals

The perinatal mortality during and after delivery in the series in which the vacuum extractor had been used was 1 5 per cent (596 VE operations) as against 4 1 per cent in the series in which forceps had been used (793 forceps operations)

That series was heterogeneous It had been collected from many departments of varying size and with different principles of obstetric care

There is a group of patients among whom delivery is relatively often completed by extraction operations, namely elderly primiparæ If application of the VE involves less risk of injury to the child than forceps the use of the former should reduce the perinatal mortality This is of course, not the only factor that influences the results of obstetric treatment The actual instrument used for extraction is only one of these factors If however the instrument offers substantial advantages this should be reflected in a series in which delivery is frequently completed by extraction It was therefore considered worth while analyzing a series

of elderly primiparæ delivered at our Department in the years 1957 to 1960

Of all deliveries in 1957, 4 were completed by forceps and 131 by VE None of the women delivered by forceps were elderly primiparæ During the years 1958 to 1960, 293 were delivered by VE and none by forceps In the series of elderly primiparæ delivered at our Department in the years 1957 to 1960, therefore only VE was used for extraction

The Series

In the years 1957 to 1960 a total of 8,817 patients were delivered at our Department Of these, 191 were 35 years of age or older, 156 were 35 to 39 years old, and 35 were 40 years or more

Of the 8,817 patients 2 2 per cent were elderly primiparæ (35 years or more)

This series was studied regarding perinatal mortality and obstetric care

Results

Table I summarizes the perinatal mortality, the frequency of Cæsarean sections and of VE-operations in the whole series and in the group of elderly primiparæ

The perinatal mortality was 2 per cent in the whole series and 2 6 per cent among the elderly primiparæ Of these deaths, 0 8 per cent and 0 5 per cent, respectively, occurred in mature infants

Table I *Perinatal Mortality and the Frequency of Cæsarean Sections and VE-operations in the Whole Series of Obstetric Cases and in a Series of Elderly Primiparæ*

	No. of Deliveries	VE (%)	Cæsarean Section (%)	Fœtal Perinatal Mortality (%)		Maternal Mortality
				Total	-500 g	
Total obstetric cases of the Department in 1957–1960	8 817	4 8	1 4	2	0 8	0
Elderly primiparæ (≧35 years) 1957–1960	191	22 5	21 4	2 6	0 5	0

Table II *Obstetric Care and Results of Treatment in a Series of Elderly Primiparæ*

	No of Deliveries	No of Children			
		Living		Dead	
		> 2,500 g.	≦ 2,500 g.	> 2,500 g.	≦ 2,500 g.
Spontaneous deliveries in cephalic presentation	100	90	5	1	4
VE-extractions	43	42	1	0	0
Cæsarian sections	41	37	4	0	0
Breech presentations	5	4	1	0	0
Duplex	2	1	3	0	0
Total	191	174	14	1	4

The obstetric care and results of treatment of 191 elderly primiparæ are given in Table II

The series was divided into the following sub-groups

(1) Simple deliveries with spontaneous delivery in cephalic presentation
(2) Deliveries completed with VE
(3) Cæsarean sections
(4) Breech presentations
(5) Twin deliveries

The series included 2 twin deliveries The number of children born was 193, of which 5 died before during or after delivery Only 1 of the children that died was delivered at term Death in that case was due to premature separation of the placenta Four of the premature infants died, 3 before, and 1 after delivery All 3 who died before delivery showed signs of maceration and 1 of them also showed multiple malformations The cause of the neonatal death of the premature infant was intracranial hæmorrhage That child like the others who died was delivered spontaneously

The series included a total of 174 full term newborn infants One of them died as mentioned, because of premature separation of the placenta This corresponds to a perinatal mortality of 0 5 per cent The figure is of the same order as that for the total of obstetric cases of the Clinic (Table I)

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(4) Breech presentations

(5) Twin deliveries

The series included 2 twin deliveries The number of children born was 193 of which 5 died before, during or after delivery Only 1 of the children that died was delivered at term Death in that case was due to premature separation of the placenta Four of the premature infants died, 3 before, and 1 after delivery All 3 who died before delivery showed signs of maceration and 1 of them also showed multiple malformations The cause of the neonatal death of the premature infant was intracranial hæmorrhage That child like the others who died was delivered spontaneously

The series included a total of 174 full term newborn infants One of them died as mentioned, because of premature separation of the placenta This corresponds to a perinatal mortality of 0 5 per cent The figure is of the same order as that for the total of obstetric cases of the Clinic (Table I)

The present series included 41 (21 4 per cent) elderly primiparæ who were delivered by Cæsarean section and 43 (22 5 per cent) in whom delivery was completed with VE In 2 cases breech extraction was performed A total of 45 per cent were delivered artificially either by the vaginal or abdominal route

Of the 35–39-year group, 23 per cent were delivered by VE and 15 per cent by Cæsarean section Of the group of patients 40 years of age or more 20 per cent were delivered by VE and 49 per cent by Cæsarean section If the 2 breech extractions are included, the proportion of women in the 35–39-year group that were delivered by artificial means was 40 per cent, and in the group of women above this age it was 69 per cent The frequency with which the women were delivered by VE, was of approximately the same order in the two groups, while the frequency of Cæsarean section in the later group was three times as high

Of the simple cephalic presentations, 143 were delivered by the vaginal route In 30 per cent of them delivery was completed with the VE The series included 43 VE operations In 25 of them the indication was uterine inertia, in 17 threatening asphyxia, and in 1 it was maternal heart failure

Of the spontaneous simple deliveries in cephalic presentation 98 out of 100 were born in the occipito-anterior position In as many as 15 of the 43 in the VE-group the presentation or position was abnormal (occipito-posterior-10, brow presentation 1, occiput-sacral-1, deep transverse arrest-3)

Cæsarean section was performed in 24 cases in the 35–39-year group In 8 of them Cæsarean section was indicated irrespective of the patient's age (inertia-4, cephalo pelvic disproportion 2, placenta prævia-1, pregnancy psychosis-1) In the remaining 16 cases the age of the mother was the most important indication Other contributory indications were noted in 14 cases (inertia-6, cephalo pelvic disproportion-3, breech presentation-1 and preceding infertility of long duration 4) That inertia or cephalo pelvic disproportion was noted as the main indication in some cases but only as a contributory indication in others depends on the relative severity of these factors in the individual case

Fifteen of the group 40 years or more were delivered by Cæsarean section The age of the patient in this group was the main indication for Cæsarean section In 5 cases there were also contributory indications (prae eclampsia 1, low placenta 1, inertia 1, several preceding miscarriages 2)

Among the infants that survived, signs of cerebral injury were noted in 3 In all of these the injury was only slight Two of them had been delivered spontaneously and 1 by Cæsarean section None of the infants of mothers in whom delivery had been completed by a VE operation showed signs of cerebral injury

Discussion

The results set forth above are better than those described in previous publications (Tables III and IV)

Of 174 full term infants only 1 died and that was due to premature separation of the placenta No infants were lost because of prolonged or difficult labour This is notable as these complications are the greatest cause of injury in the children of elderly primiparæ

The perinatal mortality among the full term newborn infants was of the same order as in the whole series of obstetric cases (Table I)

It is often difficult to say exactly what factors are decisive for the results in a given clinical series

The present series dates from the years 1957 to 1960 Most series of elderly primiparæ published by other workers date from a period when the resources of the obstetrician were by no means so good as today and they showed a higher perinatal mortality Even today a perinatal mortality which – as in the previous series – was of the same order among elderly primiparæ as in the whole series of obstetric cases must be regarded as unique

A high frequency of operative deliveries Cæsarean sections and forceps or VE operations is undoubtedly necessary for a low perinatal mortality among elderly primiparæ *Several series have* been published with equally high or higher frequencies of operative deliveries than that in the present series but these series showed a higher perinatal mortality

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Table III Perinatal (Including Premature Babies) and Maternal Mortality, Frequency of Extractions and Caesarean Sections in Different Series of Elderly Primiparæ in Earlier Publications

Author	No. of Cases	Mother's Age	Forceps %	Caesarean Section %	Mortality Perinatal %	Mortality Maternal %
Wahrsinger and Kushner (1942)	111	≥35	36.9	11.7	9.0	2.7
Erwing and Power (1943)	199	≥35	52.2	15.8	9.5	0
Kuder and Johnson (1944)	830	≥35	36.3	13.4	7.7	0.7
Randall and Taylor (1949)	250	≥35	48.8	12.8	9.2	0.4
Hamilton (1949)	108	≥35	44.4	4.6	8.3	0
Schildbach (1949)	686	≥35	14.6	12.2	6.3	1.2
Calkins (1949)	118	≥35	33.1	9.3	8.5	
Arnot and Nelson (1950)	346	>35	41.8	9.5	9.0	1.2
Waters and Wager (1950)	649	≥35	41.8	16.5	6.9	1.2
Grassi and de la Canal (1951)	185	≥30	15.6	8.1	9.2	1.1
Thompson (1951)	510	≥35	38.6	15.9	9.7	0.2
Hawkins and coll (1951)	383	≥35	50.1	16.4	4.7	0.8
Posner and Lufman (1952)	139	>35	23.4	25.1	14.1	1.4
Kolonja and Schreiner (1952)	1655[1]	≥30	5.1	2.7	7.4	0.4
	212[2]	≥30	1.9	0.9	5.2	0
Nokes and coll (1952)	201	≥35	31.4	28.8	5.4	0.5
Evans (1953)	279	≥35	22.6	6.1	4.6	2.2
Weisl (1953)	277	≥35	71.8	16.8	7.5	0.4
Hofmeister and Burgess (1955)	196	≥35	67.9	21.4	4.6	0
Williamson and Lake (1955)	107	≥35	51.4	27.9	9.9	1.9
Arthur and Kaltreider (1956)	303	≥35	75.2	14.2	4.9	0.3
Fliehr (1956)	309	≥35	61.8	10.5	11.1[3] / 5.0[4]	0.3
Kalkschmid (1957)	732	≥35	11.6	6.8	7.1	
Points (1957)	313	≥35	63.3	25.6	12.5	0.3
Schmitz and coll (1958)	277	>35	65.3	11.2	6.8	0.4
Fetzer and Klees (1959)	114	>35	4.3	8.7	12.8	
Bergman, Malmstrom, and Schoön (1961)	191	>35	22.5[5]	21.4	2.6	0

[1] 1940–1949 [2] 1950–1951 [3] 1935–1944 [4] 1945–1955 [5] Only VE-extractions

Table IV *Perinatal (Excluding Premature Babies) and Maternal Mortality, Frequency Extractions and Cæsarean Sections in Different Series of Elderly Primiparæ in Earl Publications*

Author	No of Cases	Mother's Age	Forceps	Cæsarean Section %	Mortality Perinatal	Mortality Mate
Vara (1946)	3357	≧ 30	12 5	4 3	4 3	o
Dennen and Ainsley (1951)	446	≧ 35	50.8	37 6	4.4	o
Stamer (1954)	255	≧ 36	24 0	1 5	5 0	1
Fredrikson and Anberg (1956)	408	≧ 35	17 9	14 5	3 9	o.
Bergman Malmstrom, and Schoon (1961)	174	≧ 35	24 2	21 3	0 5	o

[1] Only VE-extractions

The only demonstrable difference between the treatment in our series and that in other series is that we used a VE instead of forceps The reduction noted in the perinatal mortality must be ascribed to some extent to this replacement of forceps by VE

The choice and use of the extractor instrument used for completion of delivery must surely be of importance in a series in which 30 per cent of the vaginal deliveries are completed by extraction

In Vara s (1946) series of elderly primiparæ with mature infants 890 of the women were 35 years of age or older and 18 per cent were delivered by forceps The perinatal mortality among those delivered by forceps was 5 7 per cent The mortality due to intra cranial injury alone was 2 5 per cent in the group delivered by forceps

In a series of 70 elderly primiparæ with mature infants delivered by mid high or high Kielland forceps, Fredrikson (1956) reported 10 per cent neonatal mortality

Our VE-series includes 43 extractions 18 mid high or high, 13 low and 12 outlet extractions No children were lost in this series

The value of an extraction instrument is reflected not only in the mortality noted among children delivered instrumentally If the child dies and if one awaits spontaneous delivery or performs craniotomy it will not increase the mortality among extracted

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Hamilton (1949)	108	≥ 35	44 4	4 6	8 3	0
Schildbach (1949)	686	≥ 35	14 6	12 2	6 3	1 2
Calkins (1949)	118	≥ 35	33 1	9 3	8 5	
Arnot and Nelson (1950)	346	> 35	41 8	9 5	9 0	1 2
Waters and Wager (1950)	649	≥ 35	41 8	16 5	6 9	1 2
Grassi and de la Canal (1951)	185	≥ 30	15 6	8 1	9 2	1 1
Thompson (1951)	510	≥ 35	38 6	15 9	9 7	0 2
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	212[2]	≥ 30	1 9	0 9	5 2	0
Nokes and coll (1952)	201	≥ 35	31 4	28 8	5 4	0 5
Evans (1953)	279	≥ 35	22 6	6 1	4 6	2 2
Weisl (1953)	277	≥ 35	71 8	16 8	7 5	0 4
Hofmeister and Burgess (1955)	196	≥ 35	67 9	21 4	4 6	0
Williamson and Lake (1955)	107	≥ 35	51 4	27 9	9 9	1 9
Arthur and Kaltreider (1956)	303	≥ 35	75 2	14 2	4 9	0 3
Fliehr (1956)	309	≥ 35	61 8	10 5	11 1[3] 5 0[4]	0 3
Kalkschmid (1957)	732	≥ 35	11 6	6 8	7 1	
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and to the use of a VE instead of forceps VE-operations seem to imply less serious risks for the infants than forceps, particularly in mid high and high extraction, which are relatively common in elderly primiparæ

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infants (Randall and Taylor (1949), craniotomy in 1 2 per cent, Kalkschmid (1957) in 2 6 per cent) It is, however, possible that such a child might have been saved if we had had the instrumental resources for earlier intervention

The VE-instrument offers advantages over forceps, particularly for high and mid high extractions Inertia and prolonged labour are common complications in elderly primiparæ Instrumental intervention is therefore sometimes indicated even when the external os is not completely open and extraction with forceps is contra-indicated but VE extraction possible

If the low perinatal mortality in our VE-series differed from that in other series in which the VE-instrument has been used, one might question whether the good results were not due to chance But this can hardly be the case Judging from our experience, VE-operations appear to involve less risk for the child than forceps This is also supported by the results of our previous investigation of Swedish series collected from different hospitals The results obtained in the whole obstetric series of our Department further supports the value of the VE-operation In 1960, the VE operation was performed in 106 cases (5 per cent) in an obstetric series of 2,085 cases No child was lost during or after delivery in that VE-series

The low perinatal mortality in the present series of elderly primiparæ cannot be ascribed entirely to replacement of forceps by a VE There is, however, reason to assume that it was the extraction technique imployed that contributed considerably to the reduction of the infant mortality

SUMMARY

The authors describe a series of 191 elderly primiparæ (≧ 35 years) If the series is reduced to include only deliveries of mature infants (174 mature infants) the perinatal mortality is 0 5 per cent This figure is better than that hitherto noted in earlier publications of the perinatal mortality among elderly primiparæ The favourable figures are, in the opinion of the authors to be ascribed to the relatively high frequency of operative deliveries (21 4 per cent Cæsarean sections, 22 5 per cent VE operations)

anomalies If the cord is extremely long, there is an increased risk of prolapse, knotting, and torsion, if it is unusually short, it may rupture Vessels are more likely to rupture if their course is anomalous In velamentous insertion and interposition the vessels are protected in some measure by the membranes, but on rupture of the membranes the vessels may also rupture In *insertio funiculi furcata* the vessels are unprotected, and cases have been described in which this anomaly has resulted in fœtal death because of compression or rupture of the vessels (Herberz, 1938, Swanberg and Wiqvist, 1951) Varicosities of the umbilical cord also favour this complication

Inflammatory changes in the cord particularly vasculitis, are fairly common According to Kaufmann (1957) they occur in 2–18 per cent of all pregnancies They are histologically non specific but were formerly believed to be signs of syphilitic infection Many investigators have, however shown that such changes are not regularly demonstrable in cases of known syphilis and that they are often seen in patients in whom syphilis can be excluded with certainty

Wharton's jelly, which surrounds the vessels of the cord, consists of embryonal tissue with large amounts of mucopolysaccharides, particularly hyaluronic acid and condroitin sulphuric acid (Schoenberg and Moore, 1957) Normally this mesenchymal tissue contains at most, small amounts of collagen, but in the presence of vascular anomalies with obstruction of the artery or inflammatory changes in the vessels the tissue may show fibrosis (Browne, 1925) It has been discussed whether the vasculitis is primary or secondary to the fibrosis

Degenerative areas with accumulation of mucoids (mucoid degeneration) in Wharton's jelly are not uncommon Such degeneration may occasionally be so pronounced as to cause cyst formation One case is described below in which such mucoid degeneration gave rise to cyst formation in an otherwise uncomplicated pregnancy

Case 1 (87024/60) – A 31 year-old woman who had had one child in 1952 was delivered of her second child on Oct 13 1960 On both occasions pregnancy and delivery had been uncomplicated. Wasserman's test was negative

Bergman P Lundin P and Malmström T Acta obst et gynec Scandinav 40 37 1961

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MUCOID DEGENERATION OF WHARTON'S JELLY

An Umbilical Cord Anomaly Threatening Fœtal Life

BY

P BERGMAN, P LUNDIN AND T MALMSTRÖM

Javert (1957) called the umbilical cord the lifeline of the fœtus It is vulnerable and it is sometimes the site of developmental abnormalities and acquired changes interfering with its function and thereby threatening the life of the fœtus Pathological processes in the umbilical cord may result in early fœtal death and abortion Such changes may also lead to fœtal death during late pregnancy or delivery

A varity of umbilical cord anomalies have been described The cord may be abnormally short or abnormally long, it may be more or less rudimentary, or it may be absent

Strictures of the cord can cause complete obstruction of the blood vessels

Variations in the insertion of the cord at the placenta are relatively common, *e g* velamentous insertion, velamentous interposition, and *insertio funiculi furcata* In velamentous insertion the vessels divide in the membranes, and in velamentous interposition the vessels run in a bunch in the membranes to the placenta The vessels do not divide until they reach the edge of the placenta In *insertio funiculi furcata* the cord is inserted at the centre of the placenta, but the vessels divide short of the insertion, sometimes by as much as 10 cm

A lot of different complications are due to developmental cord

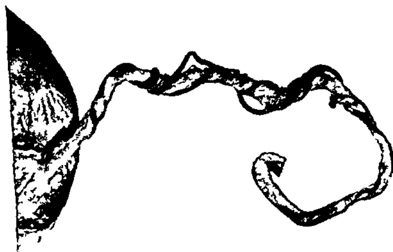


Fig 2 Case 2 Placenta with umbilical cord and arteries without Wharton s jelly

1960 She was admitted in early labour on Feb 21 and was delivered one day later The patient had not noticed any fœtal movements on the two days before delivery No fœtal sounds were audible on admission Wasserman s test was negative

The bag of waters ruptured 20 minutes before the infant was delivered The liquor amnii was green but was not blood stained

The child was born dead It weighed 2 270 g and showed no gross anomalies At autopsy the trachea and the bronchi were found to be filled with a meconium like substance and wide spread petechial haemorrhages were seen in the visceral organs particulary the pericardium. The fœtus showed no evidence of maceration The wide spread petechial haemorrhages in the internal organs were regarded as indicative of intra uterine asphyxia

The umbilical cord was of normal length (53 cm) Its point of insertion was normal *i e* in the centre of the placenta It showed a vascular anomaly the umbilical arteries along a length of some 10 cm of the cord hanging free like garlands around the cord (Fig 2) This free portion of the arteries was surrounded only by small islands of matrix tissue On the other hand the vein was enclosed in its entirety in a thin layer of Wharton s jelly

Microscopical examination of transverse sections of the cord showed that the naked muscularis of the free segment of the vessels had no adventitia or lining of Wharton s jelly (Fig 3) The layer of amnion cells was also missing

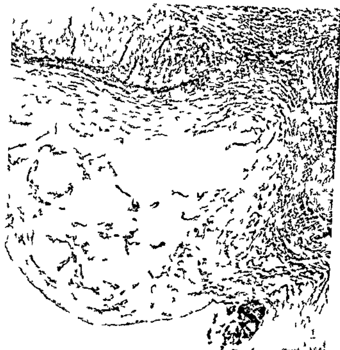


Fig 1 Case 1 Cystic lesion with mucoid degeneration along one of the arteries

The fœtus appeared healthy and weighed 3,220 g

The placenta was normal The umbilical cord showed two slack thin-walled sac like formations almost the size of chestnuts Both contained a mucous very viscous clear fluid

Microscopical examination revealed wide spread cystic degeneration of Wharton s jelly with irregular cavities filled with mucous masses (Fig 1) The larger cysts had a thin wall of mesenchymal tissue with some collagen fibres A normal layer of amnion lined the outside of the cysts and the rest of the cord The vessels were intact and showed no signs of inflamma tion *Toluidine blue and crystal violet* stained slides showed the same staining properties in the degenerative areas as in the normal tissue

In this case there was thus, advanced mucoid degeneration of Wharton s jelly, which had no demonstrable untoward effect on the fœtus

In the following case the degeneration was more extensive, there were signs of inflammatory changes in the cord and the fœtus died

Case 2 (90578/60) – The patient was a 25 year old primigravida who had last menstruated on May 11 1959 Delivery was expected on Feb 16

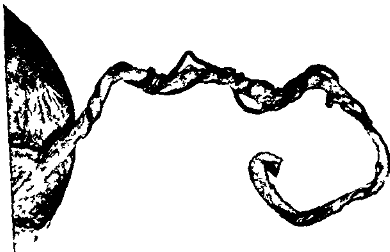


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The fœtus appeared healthy and weighed 3,220 g

The placenta was normal The umbilical cord showed two slack thin walled sac like formations almost the size of chestnuts Both contained a mucous very viscous clear fluid

Microscopical examination revealed wide spread cystic degeneration of Wharton s jelly with irregular cavities filled with mucous masses (Fig 1) The larger cysts had a thin wall of mesenchymal tissue with some collagen fibres A normal layer of amnion lined the outside of the cysts and the rest of the cord The vessels were intact and showed no signs of inflammation Toluidine blue and crystal violet stained slides showed the same staining properties in the degenerative areas as in the normal tissue

In this case there was thus advanced mucoid degeneration of Wharton s jelly, which had no demonstrable untoward effect on the fœtus

In the following case the degeneration was more extensive, there were signs of inflammatory changes in the cord and the fœtus died

Case 2 (90578/60) – The patient was a 25 year-old primigravida who had last menstruated on May 11 1959 Delivery was expected on Feb 16

The vessel walls showed an abundance of polymorphonuclear leucocytes One of the vessels was found to contain a small parietal thrombus. The outer parts of the muscularis showed areas of regressive changes with cellular disintegration and nuclear pyknosis The vessel walls were otherwise of normal structure with *sparse intramural elastic fibres* The cellular picture of Wharton s jelly was normal without signs of collagen formation. In some areas it showed small areas of mucoid degeneration of essentially the same apperance as in Case 1 (Fig 4) PAS staining according to McManus and *staining with toluidine blue* as well as with crystal violet revealed only normal staining properties

The placenta was of normal appearance No inflammatory changes were seen in the membranes or placental tissue

Discussion

The first case shows that even wide spread mucoid degeneration of Wharton s jelly need not interfere with the flow of blood through the umbilical vessels and thereby need not have any demonstrable untoward effect on the fœtus Similar cases have been described by Schmidt Elmendorff (1952) and others

The second case exemplifies an apparently rare anomaly of the umbilical cord a fairly thorough search of the literature having failed to reveal any earlier descriptions of such an abnormality The defect can hardly be ascribed to primary lack of Wharton s tissue around the vessels since normal development of the vessels is not possible in the absence of embryonal mesenchyma Nor can it be interpreted as an effect of maceration since the fœtus showed no signs of maceration In addition, the umbilical cord is usually intact even in advanced maceration of the fœtus

It cannot be excluded that the inflammatory changes in the vessel walls resulted in regressive changes and disintegration of Wharton s jelly But in uncomplicated vasculitis no degenerative changes are seen in Wharton s jelly It appears most likely that the anomaly should be conceived as advanced degeneration of Wharton s jelly of essentially the same type as in Case 1

The function of Wharton s tissue has been discussed by many investigators such as Zawisch (1955) and Patzelt (1956) Most of them believe the purpose of the jelly is to act as a supportive structure a substitute for the adventitia It protects the vessels of the umbilical cord If Wharton s tissue is maldeveloped or if the



Fig 3 Case 2 Cross section of umb l cal cord × 10



Fig 4 Case 2 Small area of muco d degeneration of adjacent ve n To the right one of the arter es Cf Fig 1 × 30

B. glin, N. E., Acta obst. et gynec. Scandinav. 40. 379. 1961

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INFLUENCE OF PROGESTERONE AND PROGESTATIONAL SUBSTANCES ON PLASMA HISTAMINASE ACTIVITY

BY

N. E. BORGLIN

The plasma histaminase activity in healthy males and healthy non pregnant females is low. During pregnancy the histaminase rises considerably and after four to five months it reaches a maximum of about 1 000 times the level in non pregnant women (Ahlmark 1944). In choriocarcinoma the plasma histaminase rises early and markedly (Willert 1952, 1961). In such cases determinations of the histaminase activity will permit an early diagnosis and thereby a better prognosis for the condition. Of other gynæcological diseases investigated the histaminase activity has been found to be raised in carcinoma of the uterine body (Borglin and Willert 1961). As a working hypothesis we assumed that the increased histaminase activity is a defence mechanism of the organism. Measures increasing histaminase activity would then increase the defence of the organism and in patients with malignant tumours possibly inhibit the growth of the tumours.

According to Swanberg (1950), injection of progesterone raises the plasma histaminase activity. It has also been shown that when large amounts of brom oxy progesterone were given to a patient with wide-spread pulmonary metastases from carcinoma of the uterine body these metastases decreased or diminished

vessels lie unprotected as in *insertio funiculi furcata* they can be compressed or they may, though rarely, rupture

It is probable that in the present case the unprotected vessels were compressed with consequent anoxia and intra uterine fœtal death The inflammatory changes may also be ascribed to the deficient protection of the vessels

SUMMARY

Two cases of wide-spread mucoid degeneration of Wharton s jelly are described In one of these cases the fœtus died

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from 50 mg every other day to 200 mg a day for 6–28 days
17 α hydroxy progesterone caproate (Proluton depot® Schering) was likewise administered i m in a dose of 500 mg distributed over 2 injections at 4 day intervals to 2 patients (1 had previously received progesterone) The other substances studied were given by mouth in the doses described below

6 methyl 17 acetoxy progesterone (Provera® Upjohn) in a daily dose of 10–15 mg for 8–14 days to 3 patients (1 of whom had previously received progesterone)

17 α ethinyl 19-nortestosterone acetate (Primolut-Nor® Schering), 10 mg daily for 10–15 days to 2 patients,

allyl œstrenol (Gestanon® Organon) in a dose of 10–30 mg daily for 7–34 days to 7 cases,

17 α methyl 19 nortestosterone (Orgasteron® Organon), in a dose of 5–20 mg daily for 7–10 days to 6 patients,

9 α bromo 11 β-ketoprogesterone (Braxoron® Squibb), 200 mg daily for 66–100 days to 3 patients with carcinoma of the uterine body

The histaminase activity was determined by the method of Ahlmark (1944) and was expressed as the amount of histamine base inactivated by 1 ml of plasma within one hour (microg /ml /hr) The normal values for this metod have been given in a previous paper (Borglin and Willert, 1961) In most of the patients examined the urinary pregnandiol was also determined before and during the treatment with the various progestional substances Pregnandiol was determined by the methods of Jensen (1955 1958)

Results

The results are given in Table I

Progesterone In none of these cases (Group A in Table I) could any increase of the histaminase be demonstrated with certainty Fig 1 shows the effect of large doses of progesterone administered for a longer period in 3 of the cases

17 α hydroxy progesterone caproate The histaminase activity in the plasma was determined before the first injection and 3 and 4 days respectively after the second injection A slight in-

(Borglin and Willert, 1961), but no increase in the plasma histaminase of the patient could be demonstrated during treatment

Histaminase occurs in large amounts in the maternal portion of the placenta, and it is believed that the histaminase demonstrable in the plasma during pregnancy is produced there (Swanberg, 1948, 1950) Decidua in non pregnant rabbits shows increased histaminase activity (Swanberg, 1950, Ahlmark and Swanberg, 1953) This decidual reaction can be induced by injection of progesterone The results could, however, not be confirmed in investigations on rats (Roberts and Robson, 1953)

The present paper is concerned with the plasma histaminase activity before, during, and after administration of progesterone and synthetic substances with a progestational effect

The Series and Methods

The series consisted of 29 patients (Table I) Most of them were post-menopausal who had been treated for different gynæcological diseases, a large number of cases of malignant disease, being also included Most of these patients had been examined during radiotherapy It is true that Balassi and Blanda (1960) reported that radium treatment increases the plasma histaminase activity, an observation which we have not been able to confirm with certainty Neither shortly before nor shortly after the determinations had the patients undergone any operation or received any other treatment that might possibly affect the histaminase activity No other hormones were given in association with progesterone or progestational agents

In 9 cases the women were of reproductive age, but it was very difficult to collect a large series of this type in which prolonged administration of progesterone or similar substances was considered justified In 3 of these 9 cases the diagnosis was acute salpingitis, in 2 progesterone was given as part of the treatment for bleeding disorders (oligomenorrhœa and metrorrhagia) in 4 treatment was given before planned laparotomy (1 case of adenomyosis, 1 of uterine myosarcoma, 1 of ovarian fibroma and 1 of carcinoma of the uterine cervix, stage 0)

Progesterone was administered i m in 9 cases in doses ranging

	D	*Allyl-oestrenol*		20	15	300	0.0114	0.0104	0.8	—	1.2
21	32	Carcinoma of cervix stage 0	16	30	10	300	0.0095	0.0116	1.1	—	0.4
22	69	Fibroma of the ovary		10	11	110	0.0116	0.0135	—	—	—
23	35	Adenomyosis of uterus		20	10	200	0.0135	0.0083	0.6	—	0.7
				20	7	140	0.0126	0.0095	1.5	—	1.6
24	38	Oligomenorrhœa	38	20	10	200	0.0189	0.0126	—	—	—
25	80	Endometrial adenocarcinoma									
26	53	Metropathia hæmorrhagica cystica	1	20	34	680	0.0093	0.0074	0.6	—	0.6
	E	*17 methyl 19-nortestosterone*									
12	59	Endometrial adenocarcinoma	7	15	10	150	0.0126	0.0356	0.6	—	1.1
13	63	Endometrial adenocarcinoma	17	5	9	45	0.0093	0.0221	0.4	—	1.9
14	62	Endometrial adenocarcinoma	19	20	7	140	0.0230	0.0483	—	—	—
15	17	Metrorrhagia		5	8	40	0.0084	0.0021	2.4	—	1.3
16	48	Fibroma of ovary		20	8	160	0.0208	0.0126	—	—	—
17	74	Carcinoma of cervix stage I	28	20	10	200	0.0105	0.0221	0.7	—	1.2
	F	*17 α hydroxy progesterone caproate*									
1	64	Carcinoma of ovary?	24	250	2.4	500	0.0116	0.0137	0.8	—	1.4
18	51	Carcinoma of stomach	5	250	2.4	500	0.0020	0.0030	2.3	—	2.6
	G	*9α bromo-11 β ketoprogesterone*									
27	70	Endometrial adenocarcinoma	20	200	66	15 500		0.0167	—	—	1.8
28	66	Endometrial adenocarcinoma	18	200	96	19 200	—	0.0231	—	—	2.0
29	55	Endometrial adenocarcinoma	4	200	100	20 000	—	0.0116	—	—	1.7

Table I *Effect of Progesterone and Progestational Substances on Histaminase Activity in Plasma*

Case No	Age in Years	Diagnosis	Number of Years After Menopause	Dose per Day mg	No of Days	Total Dose mg	Plasma Histaminase micros /ml /hr		Pregnandiol, mg /24 hr		
							Before Therapy	At End of Therapy	Before Therapy	During Therapy	At End of Therapy
	A *Progesterone*										
1	64	Carcinoma of ovary?	24	50	9	450	0.0137	0.0062	1.4	—	8.2
2	80	Carcinoma of ovary	30	50	4/7	200	0.0041	0.0062	1.3	—	2.8
3	52	Carcinoma of ovary	3	100	19	1 900	0.0041	0.0095	2.3	18.0	—
4	42	Myosarcoma of uterus	—	100	19	1 900	0.0242	0.0210	0.4	30.6	25.4
5	68	Endometrial adenocarcinoma	30	100	10	1 000	0.0125	0.0113	—	—	—
				200	6	1 200	0.0113	0.0135	—	—	—
6	18	Acute salpingitis	—	100	28	2 800	0.0116	0.0126	0.8	16.8	5.1
7	77	Endometrial adenocarcinoma	25	100	12	1 200	0.0084	0.0092	0.3	—	10.9
8	24	Acute salpingitis		100	8	800	0.0095	0.0116	—	—	—
9	20	Acute salpingitis		100	12	1 200	0.0082	0.0093	0.7	—	19.1
	B *6-methyl 17 α acetoxyprogesterone*										
4	42	Myosarcoma of uterus		15	8	120	0.0126	0.0105	1.0	—	2.0
10	62	Endometrial adenocarcinoma	22	10	14	140	0.0284	0.0273	1.2	—	0.6
11	60	Post menopausal bleeding	5	10	12	120	0.0189	0.0168	1.5	—	0.3
	C *17-α ethinyl 19-nortestosterone acetate*										
19	74	Diverticulitis of colon	24	10	15	150	0.0104	0.0135	—	—	—
20	52	Carcinoma of cervix stage III	5	10	10	100	0.0095	0.0083	0.2	—	0.3

monary metastases Unfortunately the histaminase activity was not determined in these cases before the beginning of treatment but in 2 of the cases (Nos 27 and 29) the histaminase, after very large doses of brom oxy progesterone, lay within the normal range of variation In the third case the activity was above the upper limit of the normal range, but such values are often seen in cancer of the uterine corpus (Borglin and Willert, 1961) In this case the histaminase activity was determined again ten months after withdrawal of therapy and then the value found was much lower, 0 0125 microg/ml/hr Such decreases are also seen in patients treated (radiotherapy and/or surgery) for carcinoma of the uterine body independently of previous progesterone treatment

17 a methyl 19 nortestosterone Continuation of this treatment with large doses was avoided because of the risk of virilization In 4 of the cases (Group E in Table I) the histaminase activity rose above the upper limit of the normal range of variation All of these 4 patients had received treatment because of cancer, 3 because of carcinoma of the uterine body and 1 because of carcinoma of the cervix stage I In 2 cases in which no increase could be demonstrated both patients had benign diseases (metrorrhagia and benign fibroma of the ovary, respectively) and were younger than the others in that group Fig 2 gives the histaminase activity in the 6 patients belonging to this group

The urinary pregnandiol was increased only after treatment with progesterone the other substances studied appeared to be metabolized to other compounds or eliminated in some other way

Discussion

The physiology of histaminase and of histamine is not properly understood Histaminase has been shown in varying amounts in all organs It is often fairly abundant in the adrenal cortex in the liver and in the digestive tract and then particularly in the mucosa of the small intestine (Hæger and Kahlson, 1952 a) In cats dogs and rabbits the histaminase activity is much higher in thoracic duct lymph than in the plasma (Carlsten, 1950 a) Its occurrence has often been related to the inactivation of histamine in the body but no convincing evidence has been pre-

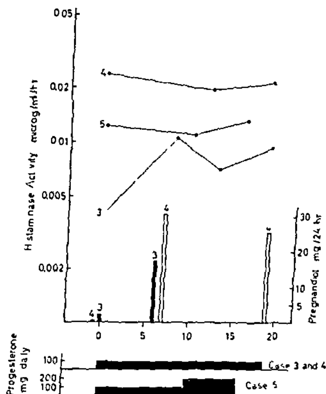


Fig 1 Plasma histaminase activity in Cases 3, 4 and 5 during administration of progesterone From above plasma histaminase, urinary pregnandiol and dose of progesterone given Figures denote case numbers

crease lying within the normal range of variation was noted (Group F in Table I)

17-a ethinyl-19 nortestosterone acetate On treatment with this substance the histaminase was approximately the same before and after treatment (Group C in Table I)

Allyl-œstrenol was given to 6 patients Large doses over a long period (20 mg daily for 34 days, Case 26) produced no demonstrable change in the histaminase (Group D in Table I)

6 methyl-17-a acetoxy-progesterone The plasma histaminase activity was regularly lower after administration, but the decrease was only slight (Group B in Table I)

9-a-bromo-11-β ketoprogesterone (Group G in Table I) In one of the cases (No 29, reported previously by Borglin and Willert, 1961) a remarkable reduction was noted in the pul-

high production of histamine (Kahlson *et al*, 1959, c) If the production of histamine in the rat is *inhibited by histidine decarboxylase inhibitors* (semicarbazide) and by pyridoxine deficiency the elaboration of histamine may be reduced to about 20 per cent of normal The fœtal growth is arrested, the fœtus dies and becomes mummified (Kahlson and Rosengren, 1959) The increased production of histamine has been related to growth This hypothesis has found support by Kahlson and co-workers (Kahlson and Rosengren, 1959, a, Kahlson *et al*, 1960 b) who also showed that the synthesis of histamine is increased after partial hepatectomy and during wound healing The increased activity in the histaminase during pregnancy may therefore possibly be a manifestation of an attempt of the organism to neutralize an increased formation of histamine

The histaminase activity in different tissues seems to depend on various factors Adrenalectomy in cats is followed by a rapid decrease of the total histaminase (Hæger and Kahlson, 1952, b) and hypophysectomy results in depletion of the depots (Hæger *et al*, 1953) An increase of the histaminase activity in the thoracic duct lymph (Carlsten, 1950, b Carlsten and Wood 1951) could also be demonstrated This release of histaminase from the depots in the intestine and kindneys can be prevented by administration of adreno-cortical extract (Carlsten and Wood 1951 Hæger, 1953) The blood plasma on the other hand shows no increase in the histaminase activity in these experiments (Carlsten 1950, b) Injection of progesterone into rabbits increased the histaminase content in the endometrium even in spayed animals (Swanberg 1950 Ahlmark and Swanberg 1953) The histaminase activity in the decidua is also increased in pseudo-pregnancy but this increase does not occur if the animals are spayed after copulation Gonadotrophins had the same effect as progesterone on intact animals and the administration of testosterone also produced an *increase* in the histaminase activity of the endometrium Œstrogens on the other hand had no effect Cazzola (1954) confirmed the results of administration of progesterone in investigations on rats while Roberts and Robson (1953) were unable to demonstrate any effect of the œstrogenic hormone progesterone des-

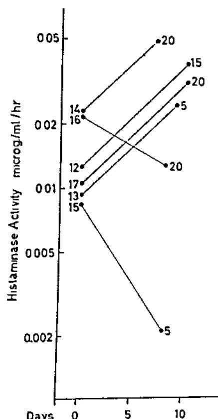


Fig 2 Plasma histaminase activity during administration of 17-α methyl 19 nortestosterone in Cases 12 to 17 Figures to left indicate case numbers Figures to right denote the daily dose of 17 α methyl 19 nortestosterone in mg

sented High histaminase activity does not necessarily imply low histamine concentration, and *vice versa* (Heger and Kahlson, 1952, a) The occurrence of histaminase varies widely from species to species Investigations of the effect of various factors on the histaminase activity in the human body must therefore be studied in man

Kahlson and co-workers (1958, 1959, 1960) have shown that increased amounts of histamine are excreted in the urine of rats during pregnancy This increased excretion of histamine seems to be due to a rapid turnover of histamine in the fœtus and particularly in the fœtal liver tissue (Kahlson *et al*, 1960, a) In human fœtuses there also appears to be a relatively

high production of histamine (Kahlson *et al*, 1959 c) If the production of histamine in the rat is inhibited by histidine decarboxylase inhibitors (semicarbazide) and by pyridoxine deficiency the elaboration of histamine may be reduced to about 20 per cent of normal The fœtal growth is arrested, the fœtus dies and becomes mummified (Kahlson and Rosengren, 1959) The increased production of histamine has been related to growth This hypothesis has found support by Kahlson and co-workers (Kahlson and Rosengren, 1959 a, *Kahlson et al*, 1960 b) who also showed that the synthesis of histamine is increased after partial hepatectomy and during wound healing The increased activity in the histaminase during pregnancy may therefore possibly be a manifestation of an attempt of the organism to neutralize an increased formation of histamine

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oxy corticosterone acetate or testosterone on the histaminase activity in the rat uterus These authors claimed that the increase in histaminase in the rat uterus during pregnancy was not due to any hormonal effect

Swanberg (1950) showed an increased plasma histaminase activity in 2 women with chronic salpingitis following progesterone therapy These results have been criticized (Kapeller-Adler, 1951, Andreoli and Della Porta, 1956) After i m injection of 50 mg progesterone in oil into 10 pregnant women in the 5th and 9th months of pregnancy Andreoli and Della Porta found, however, a brief decrease in the serum histaminase Swanberg's results could not be confirmed in the present investigation either In no case treated with progesterone was any increase found in the plasma histaminase The fluctuation observed in the individual daily variations was within the limits of the normal range, and partly within the error of the method This also applies to other progestational compounds studied with the exception of methyl nortestosterone, which produced a marked increase in 4 out of 6 cases This substance has, however, not only o progestational effect, it has an androgenic, anabolic, and anti-gonadotrophic effect and inhibits the adrenal cortex (for references, see Borglin, 1960) The increased histaminase activity in the plasma during pregnancy may be due to hormonal influences other than that of progesterone This is supported by the lack of any effect of progesterone and the effect of methyl-nortestosterone might indicate which endocrine factors are likely to be responsible The fact that adrenalectomy in animals results in depletion of histaminase depots is compatible with the assumption that it is the inhibitory effect of methyl-nortestosterone on the adrenal cortex that is the active principle

The possibility cannot be excluded that progesterone increases histaminase in the depots and thereby lowers the histaminase activity of the plasma This possibility will be the subject of later investigations

The determinations of urinary pregnandiol have confirmed that only progesterone produces an increase in the excretion of pregnandiol Other substances studied are excreted as other

degradation products and this also appears to hold for the closely related 17 hydroxy progesterone caproate

SUMMARY

In a series of 29 women the activity of histaminase in the plasma was studied before and during administration of progesterone, 17 hydroxy progesterone caproate, allyl-œstrenol, 17 methyl 19 nortestosterone, 17 ethinyl 19 nortestosterone acetate, methyl acetoxy progesterone and brom oxy progesterone The following observations were made

(1) Progesterone does not increase the plasma histaminase activity

(2) This holds also for the other substances studied with the exception of methyl 19 nortestosterone which in 4 of 6 patients studied produced a marked rise

These observations and those made by earlier workers are discussed, and it is suggested that histaminase activity in the tissues and plasma is at least partly influenced by hormones

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TISSUE CULTURE STUDIES ON HUMAN OVARIAN TUMOURS WITH SPECIAL REFERENCE TO THE INFLUENCE OF ŒSTROGENS AND ANDROGENS ON THE GROWTH RATE

BY

STIG KULLANDER AND BENGT KÄLLÉN

Introduction

The *in vitro* cultivation of tumour cells from various sources has been used as a tool for the analysis of cellular biology The present authors and co-workers have investigated the response to endocrine treatment *in vitro* of various human and animal tumours Kullander and Källen (1959) showed that the cell growth from ovarian tumours induced in rats by intra splenic grafting could be arrested by androsterone and to a lesser extent by œstrone and progesterone In a later paper (1961), it was further shown that during the life span of a tumour and after isotransplantation to hosts of various endocrine status such tumours changed their properties as tested in tissue culture In the present investigation such studies are presented carried out by similar methods on spontaneous human ovarian tumours of various types

The value of endocrine therapy in the treatment of advanced ovarian carcinoma is debatable According to some authors (cf Husslein 1954 Runge 1959) androgen therapy is to be recommended in these cases On the other hand Prediger (1951),

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Material and Methods

Fourteen human ovarian tumours have been studied (Table I) Pieces of the tumours were removed at operation, placed in prewarmed Tyrode s solution, and taken to the tissue culture laboratory Culturing commenced within one hour after the excision of the tumour

The biopsies were divided into two parts one for histologic study and one for culturing purposes The latter was cut into small explants, measuring approximately 1 mm³, which were plased in plasma clots in Carrel flasks (D5) The clots consisted of 50 per cent unheparinized cockerel plasma and 50 per cent chick embryo extract diluted to 5 per cent with Tyrode s solution to which the hormones had been added Total volume of the clot was 1 0 ml The hormones studied were androsterone and œstrone (Sigma) They were dissolved in stock solutions of 96 per cent alcohol in a concentration of 5 and 3 mg./ml respectively In control cultures, corresponding amounts of pure alcohol were added The final alcohol concentration in the clot was 0 25 per cent, giving final hormone concentrations of 12 5 (androsterone) and 7 5 (œstrone) μg/ml The following day a fluid phase of 1 ml of human serum, obtained from healthy blood donors was added

For registering the growth rate of the cultures the method adopted by Kullander and Källen (1959) was used The cultures were drawn each day with the aid of a drawing apparatus magnification 23 ×, and the culture areas were determined planimetrically For each culture an exponential growth function could be calculated from these figures and after logarithmation a straight line graph was obtained The growth rate of the culture was determined as the angle coefficient of this line The means obtained for the cultures of each experimental group were then compared by t tests

The percentage of growing cultures was also registered for each experimental group and differences were tested for significance by corrected chi square tests

even when using large doses of androgens, could find no effect on the growth of human ovarian tumours or their metastases, or on their sensitivity to X-rays. Haas and Verhagen (1954) also stated that androgen therapy is of little value in these cases. They treated 11 women who had had partial resections of ovarian carcinomas and in no case was regression of the tumour observed. On the other hand, Kohler (1952) observed that a case of ovarian carcinoma did not respond to androgen therapy, but showed marked regression after combined androgen and œstrogen therapy.

Steroids may act directly on the tumour cells or *via* the hypophysis. There is also, however, a general effect on the metabolism of the patient, whose general condition is often seen to improve without any objective signs of tumour regression. The hormone treatment also sometimes produces a euphoric effect, which is of some value (cf. Weghaupt 1957). Kottmeier (1951), referring to the use of testosterone propionate on ovarian carcinoma, stated that '*it has been of considerable value. We do not believe that the male hormone will have any influence on the carcinoma but it improves remarkably the general condition of the patient*.'

Inhibition of tumour growth by steroid therapy may be brought about indirectly by depression of hypophyseal function or directly by arrest of cellular growth. The latter factor can be studied in tissue culture. The authors have therefore studied the growth of human ovarian tumours in tissue culture and in some cases the growth rate has been measured and compared in control cultures and in cultures containing androgen or œstrogen.

Literature on the culture of human ovarian tumours is limited, and only Ivers, Pomerat and Neidhardt (1948) and Rose, Townsend, and Pomerat (1951) have studied the possible influence of steroids on their growth. Ivers *et al.* described a case of an ovarian carcinoma with ascites, and cultured ascitic cells in order to study their reaction to steroids. A possible arresting effect of androsterone and progesterone was noted. Rose *et al.* studied one case of Brenner tumour and 2 cases of ovarian carcinoma. Neither œstrone nor androsterone influenced the growth rate of the cultures.

Material and Methods

Fourteen human ovarian tumours have been studied (Table *I*) Pieces of the tumours were removed at operation, placed in pre warmed Tyrode s solution, and taken to the tissue culture laboratory Culturing commenced within one hour after the excision of the tumour

The biopsies were divided into two parts one for histologic study and one for culturing purposes The latter was cut into small explants, measuring approximately 1 mm^3, which were plased in plasma clots in Carrel flasks (D5) The clots consisted of 50 per cent unheparinized cockerel plasma and 50 per cent chick embryo extract diluted to 5 per cent with Tyrode s solution to which the hormones had been added Total volume of the clot was 1 0 ml The hormones studied were androsterone and œstrone (Sigma) They were dissolved in stock solutions of 96 per cent alcohol in a concentration of 5 and 3 mg /ml respectively In control cultures corresponding amounts of pure alcohol were added The final alcohol concentration in the clot was 0 25 per cent, giving final hormone concentrations of 12 5 (androsterone) and 7 5 (œstrone) µg/ml The following day a fluid phase of 1 ml of human serum, obtained from healthy blood donors was added

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The percentage of growing *cultures was also registered* for each experimental group and differences were tested for significance by corrected chi square tests

Table I *Data on Human Ovarian Tumours Studied in vitro*

Case	Age	Past History	Histology	*In vitro* Growth Pattern	Effects of Steroids *in vitro*	
					Androsterone	Œstr a
A M	53	Post menopausal, no pathological bleeding	Pseudomucinous cystadenoma	Mainly epithelial		o
B P I	51	Last year irregular bleeding	Pseudomucinous cystadenoma	Epithelial	o	o
B P II	53	Post menopausal, recent slight bleeding	Pseudomucinous cystadenoma	Epithelial + pseudoreticular	o	−
E L	49	Regular menstruation	Pseudomucinous cystadenoma	Epithelial, mainly pseudoreticular	+	+
S R	26	Regular menstruation	Papillary pseudomucinous cystadenoma	Pseudoreticular + nearly reticular	o	+
F S	66	Post menopausal, no pathological bleeding	Serous cystadenoma	Epithelial		
I R	68	Post menopausal, no pathological bleeding	Papillary serous cyst adenoma	Epithelial		
O B	67	Post menopausal, no pathological bleeding	Cystadenofibroma	Epithelial + pseudoreticular	o	
J P	73	Post menopausal no pathological bleeding	Cysto-carcinoma	Pseudoreticular + a little epithelial		
V L	57	Post menopausal no pathological bleeding	Papillary cysto-carcinoma	Pseudoreticular		
H O	60	Post menopausal no pathological bleeding	Cysto-carcinoma	Pseudoreticular + nearly reticular	o	+
A A	53	Slight bleedings a few months	Papillary cysto-carcinoma	Epithelial (irregular)		
H A	56	Post menopausal 2 weeks moderate bleedings	Solid carcinoma	Isolated cells		
E R	49	No menstruation last 2 months	Solid carcinoma	Pseudoreticular		

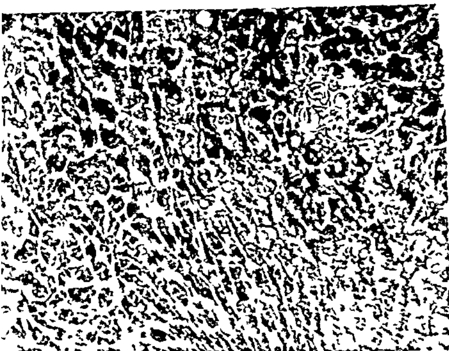


Fig 1 Phase-contrast photomicrograph of cells grown from human ovarian tumour B F II taken 7 days after culturing Note dense epithelial mat of closely packed small cells × 275

Results

Growth Pattern

In the cultures prepared from ovarian tumours cell outgrowth occurred in various patterns Following the nomenclature used by Röhl (1959) in his studies of the growth pattern of human prostatic carcinomas an epithelial growth pattern and a pseudo-reticular one can be distinguished In the former pattern, the cells are arranged in regular sheets of polygonal cells In some cases the cells are small and densely packed (Fig 1) in others they are bigger and slightly more scattered (Fig 2)

In a typical pseudo-reticular growth pattern (Fig 3) the cells

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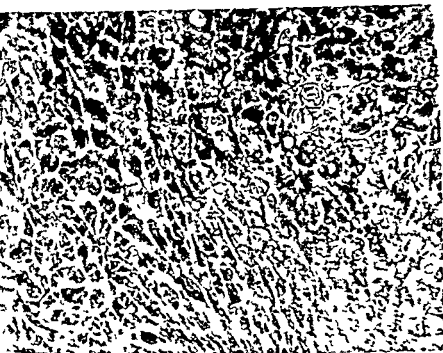


Fig 1 Phase-contrast photomicrograph of cells grown from human ovarian tumour B P II, taken 7 days after culturing Note dense epithelial mat of closely packed small cells × 275

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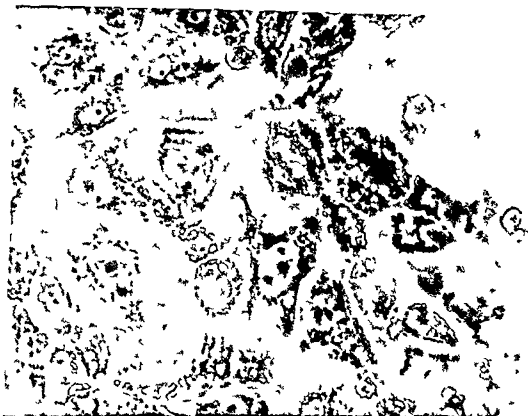


Fig 2 Phase-contrast photomicrograph of cells grown from human ovarian tumour A. A taken 5 days after culturing Note large epithelial cells with granulated cytoplasm large nucleoles arranged in a continuous cell mat × 275

form thick trabecules within which the relatively small but spindle formed cells lie closely packed In many cases a dense epithelial mat is partially broken up into such trabecules (Fig 4)

In some tumours the reticular type is still more pronounced and the cells are more scattered irregular in size and shape some rather resemble fibroblasts (Fig 5)

Typical fibroblastic growth can also be seen in parts of many cultures

Among the 8 benign ovarian tumours cultured 6 were dominated by an epithelial growth pattern 1 contained epithelial parts but was dominated by a pseudo reticular growth and 1 grew with a pure pseudo reticular growth pattern Of the 6 malignant tu



Fig 3 Phase-contrast photomicrograph of cells grown from human ovarian tumour J P taken 3 days after culturing Note arrangement of cells into typical pseudo- eticular formations × 275

mours 1 showed epithelial growth of large irregular cells con taining large nucleoles and cytoplasmic granulation and vacuolization (cf Fig 2) 4 grew according to the pseudo-reticular pattern and 1 nearly reticular

Influence of Steroids on Growth Rate

Eight cases showed sufficient growth to permit endocrine testing *in vitro*

The results of the quantitative measurements on the growth rate of the ovarian tumours in control androsterone-treated and testrone-treated cultures are given in Table II

Table II *Growth Rate in vitro of Human Ovarian Tumours*

Case	Group	n_{Total}	$n_{Growing}$	Mean Growth Rate	Sum of Squared Deviations	t	P
A M	C	19	10	0.128	0.0189		
	O	20	15	0.096	0.0598	0.9	0.3–0.4
B P I	A	12	8	0.120	0.0200	0	1.0
	C	13	11	0.120	0.0156		
	O	12	10	0.134	0.0072	0.9	0.3–0.4
B P II	A	18	10	0.151	0.0587	0.7	≈ 0.5
	C	18	14	0.145	0.0372		
	O	18	14	0.161	0.0799	2.1	≈ 0.05
E L	A	12	6	0.140	0.0028	4.7	0.01–0.001
	C	11	4	0.058	0.0031		
	O	12	8	0.121	0.0110	2.7	0.02–0.05
S R	A	36	32	0.069	0.0312	0.1	> 0.9
	C	36	36	0.068	0.0233		
	O	36	33	0.084	0.0321	2.0	0.02–0.05
O B	C	16	10	0.103	0.0555		
	A	16	11	0.112	0.0356	0.27	0.7–0.8
H O	A	18	6	0.054	0.0023	1.1	≈ 0.3
	C	18	13	0.045	0.0017		
	O	18	15	0.059	0.0059	2.0	≈ 0.05
E R	A	18	7	0.082	0.0129	0.6	0.5–0.6
	C	18	10	0.094	0.0121		
	O	18	4	0.079	0.0031	0.7	≈ 0.5

A, androsterone, containing cultures, C control cultures O, oestrone-containing cultures t tests were made between control group and hormone-treated group n number of cultures in each group

Table II shows that a strong stimulating effect was seen with androsterone in 1 case (Case EL – a benign pseudomucinous cystadenoma), the other cases tested with androsterone showed no response With oestrone, stimulation was seen in 4 cases – 3 benign pseudomucinous cystadenomata (BPII EL and SR) and



Fig 4 Phase-contrast photomicrograph of cells grown from human ovarian tumour A M taken 8 days after culturing Note epithelial mat partially broken up into cell beams × 275

one carcinoma (HO) the latter being a cysto-carcinoma without signs of metastasis

In no case was there a significant difference in the percentage of outgrowth obtained in control and steroid treated groups In two cases ER and HO there was an indication of a lower out growth percentage in experimental groups but a x^2 test showed that it was of no statistical significance ($x^2 = 2\ 88$ and $2\ 73$ at 1 d f resp)

Discussion

The outgrowth pattern of the ovarian tumours studied shows a condition similar to that found by Rohl (1959) in prostatic carcinoma the benign tumours grew with a dominating epithelial



Fig 5 Phase contrast photomicrograph of cells grown from human ovarian tumour H O taken 11 days after culturing Note scattered irregular cells, some with large nucleoles, some with strongly granulated cytoplasm × 275

growth pattern, the malignant ones, especially poorly differentiated ones, grew with a pseudo reticular and reticular pattern The cysto carcinoma of Case AA however, showed epithelial mats of regular cellular arrangement but the cells that grew were extremely polymorphic, and their cytological appearance showed characteristics usually regarded as typical of malignant cells

The hormone dependence demonstrated *in vitro* could be found in half of the benign tumours and in 1 one of the 2 malignant tumours Stimulation resulted from androgens in one case and from œstrogens in the remaining cases Steroids did not result in apparent arrest of growth of cells in any case Whatever the possible effect of gonadotrophins may be on the growth of cells

of this nature, no direct beneficial effect of the steroids on the growth of ovarian tumour cells can be expected

Two cultures were taken from women still menstruating In both, a stimulating effect of œstrone was found Four cultures were from tumours in post menopausal women without any pathological bleeding In 3 of these, no hormone response *in vitro* could be found (1, however, was not tested with œstrone) in the fourth, stimulation occurred with œstrone Finally 2 patients had pathological bleeding and in 1 of these œstrogen stimulation was seen *in vitro* Our series is too small to permit any conclusions of a possible relationship between the endocrine status of the patient and the *in vitro* behaviour of the tumour cells

If these findings are compared with those previously published by the present authors on experimental rat ovarian tumours it is interesting to note that œstrogen stimulation of ovarian tumour cells can be seen *in vitro* both in human and rat material In the latter, the findings *in vitro* correspond to a similar condition *in vivo* (Kullander and Källen 1961) *In vitro* investigations of human tumour material may therefore be of interest for therapeutic considerations in these cases

SUMMARY

Tissue culture studies have been made of 14 human ovarian tumours benign and malignant Their outgrowth patterns have been described and the possible influence of steroids on their growth rate has been studied Eight of the tumours were tested with œstrone or androsterone or both Four showed signs of œstrogen stimulation 1 of androgen stimulation also 3 of the reacting tumours were benign A comparison is made with previously published investigations of a similar nature on rat ovarian tumours and it is stressed that a possible way of judging endocrine responsiveness of ovarian tumours is to be found in tissue-culture methods

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CYSTOMETRIC EXAMINATION OF PATIENTS TREATED FOR CANCER OF THE UTERINE CERVIX BY IRRADIATION

BY

T RAUTALINKO AND O WIDHOLM

The high incidence of urological complications and their decisive role as a cause of death in patients with cervical cancer has long been recognized It is only in the last few years, however, that the relevant problems have received greater attention and a large number of deaths have resulted not from recurrence of cancer but from post operative or post irradiation cicatrization and fibrosis of the parametrial connective tissue followed by urinary stasis and uraemia Kirchoff (1960) reported on findings by Stolte and Schultz Stolte performing autopsies on 82 irradiated cervical cancer patients, found that in 41 the cause of death was a complication in the urinary tract uretero-stenosis and hydronephrosis while in 10 cases death was caused by cicatrizations without re activation of cancer Schultz from 109 autopsies, attributed death in 27 cases to a complication in the urinary tract, and in 8 cases to fibrosis of the parametrial tissue without reactivation of cancer One might also mention the report by Bockler and Prinz (1959) of the series of 150 patients with carcinoma of the cervix treated surgically or by irradiation Autopsy revealed no recurrence of cancer in the true pelvis or elsewhere in the body in 19 3 per cent of the series though the majority showed

considerable changes in the urinary tract V Garrelts (1960) reported on 16 patients with post-irradiation hydronephrosis treated in a specialized urological clinic, only two of these cases were attributable to the spread of carcinoma Burns *et al* (1960) found that 27 3 per cent of their patients with cervical cancer developed hydronephrosis as a result of treatment The same authors emphasize the great prognostic significance of confirmed hydroureteronephrosis

The studies to date have mostly dealt with the morphological changes found in the urinary tract after treatment, while little attention has been devoted to the study of the functioning of these organs, especially after irradiation therapy Lindholm (1960) measured the bladder volume of a series of 28 patients treated by irradiation and suffering from disturbances of micturition, and was convinced that grossly contracted bladders in patients with uterine or ovarian cancer were not the result of irradiation therapy Muth s series in 1958 consisted of 300 irradiation-treated cervical carcinoma patients without relapse His enumeration of the urological methods of examination does not include cystometry, though he mentions that cystometry was performed in 102 cases, nor does he present any control material The only report we have traced on cystometry used systematically to assess post irradiation functional changes of the bladder was written by Naujoks (1959) His series consisted of 24 patients with irradiation treated cervical carcinoma, clinically free from relapse, on whom cystometry was performed prior to and immediately after treatment

Case Material and Methods

The series consisted of 68 patients with cancer of the uterine cervix, grades I–III, clinically free from relapse They were divided into the following groups Group I those in whom less than one year had elapsed since the beginning of treatment 24 patients, Group II, those in whom 1–3 years had elapsed since the beginning of treatment 16 patients Group III, those in whom more than 3 years had elapsed from the beginning of treatment, 16 patients The control Group E consisted of 10 patients in whom

cancer of the uterine cervix, grades I–III, had been diagnosed, in whom cystoscopy had revealed no bladder changes, and who were later treated by irradiation Two further cases are also reported on, both from Group II, one had in addition an acute urinary tract infection and the other was found, on cystoscopy, to have papilloma of the bladder

The importance of cystometry has often been emphasized, most recently by Youssef (1956), but one of the reasons why it has not been more widely adopted is the great variety of equipment available Povlsen (1943) remarked, as early as 1943, that he had in comparatively recent years found 22 more or less independent methods of performing cystometry, and recommended two different devices without comparing the results obtained with them Youssef (1956) and Naujoks (1959) in their investigations used the equipment described by Hartl (1953) which in the opinion of the present writers allows a rapid examination but leaves room for improvement in accuracy

At the outset of this study, no self recording cystometer was known to be in clinical use in Finland though one has recently been purchased for the Women s Clinic The equipment employed by the writers had a graded bottle containing 0 9 per cent NaCl solution suspended at a height of approximately 180 cm This was connected by a fluid transmission flask to an opened Foley s catheter and after evacuation of the bladder, the solution, at a temperature of 20 C and at a rate of 200 drops per minute was allowed to pass into the bladder through the thinner tube of a two-way catheter The thicker tube of the catheter was connected by a tube 5 mm in diameter to an ascending glass tube graded in centimetres Apart from Foley s catheter every piece of the equipment was transparent and it was easy to see if there were air bubbles The zero point for the measurement was selected in the usual way and consisted of the height of the upper border of the symphysis on the grading of the ascending tube the grading again was accurately measured in the fluid tube on the principle of joining vessels Since care was taken to retain the fluid level in the drop chamber of the fluid transmission flask (i e the hydrostatic pressure bearing on the bladder) unchanged for every examination the equipment could provide results that

may be considered comparable It also has other advantages over the equipment described by Hartl (1953) the flow of fluid into the bladder is even and accurate, it need not be interrupted when the readings are taken, and any reflective contractions occurring in the bladder may also be recorded without interruption One disadvantage is the slowness of our equipment compared with Hartl's

During the measurement, a note was made of the height of the fluid column in the ascending tube after each 50 ml On the basis of these readings, a curve, the cystometrogram, was plotted A note was also made of that phase of the bladder filling at which the patient for the first time felt urinary urgency (M_1) as well as that at which the urinary urgency became compulsive (M), and these readings were entered on the curve Finally, a recording was made of the so-called reflective micturition pressure, i e the pressure observed when the detrusor muscles of the bladder contracted (when the patient was asked to urinate through the catheter by relaxing the perineal muscles), and the so-called maximal micturition pressure when the patient contracted the superficial abdominal muscles for ejection

The results are presented, by group, in the form of a mean value curve (Fig 1)

The changes in the reflective and maximal micturition pressure are given in Table I

To demonstrate the possibilities of the method employed the two special cases were plotted in addition to the Group II mean value curve The curves obtained are seen to differ completely in type (Fig 2)

Results

Changes were noted in the patient s cystometrogram after irradiation therapy Both the minimal (M_1) and the maximal (M_2) urinary urgency show a move to the left in addition the tone of the bladder increases, as is distinctly shown in the steeper upward sweep of the curve in other words the basic shape of the curve is changed Furthermore, changes are noted in micturition pressures Povlsen (1943) found on repeating his examinations on the same patients that the degree of bladder filling at

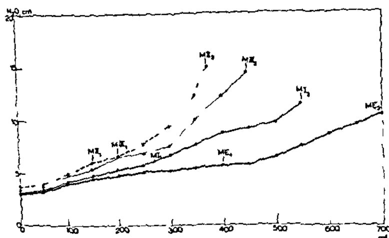


Fig 1 ——— Group E control series 10 patients ——— Group R I one year after treatment 24 patients - - - - Group R II 1–3 years after treatment 16 patients Group R III 3 years after treatment 16 patients

Table 1 *Reflective and Maximal Micturition Pressures in the Different Groups*

Group	E	I	II	III
Reflective micturition pressure cm	25	34	44	34
Maximal micturition pressure cm	46	55	67	65

the minimal and maximal urinary urgency might vary although differences seldom exceeded 100 ml The type of bladder function i e the basic form of the curve does not however change on repeated examinations but is often identical For this reason it was assumed that the changes noted were not indications of individual variation but a result of irradiation therapy

A comparison of the mean value curves for Group E and Group I shows that the results agree with those obtained by Naujoks (1959) in the shift to the left of the M_1 and M_2 points Since he however has not presented his results in the form of a curve a form of expression which Povlsen (1943) finds more reliable – no further comparisons can be made Muth contents himself

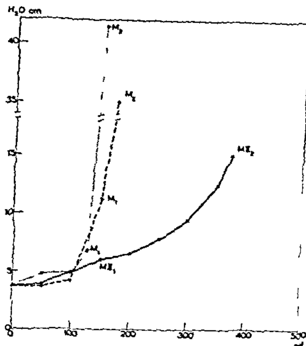


Fig 2 ——— Group II, 1–3 years after treatment, mean value curve, - - - - Group II, papilloma vesicae urinalis 1 patient, Group II pyelocystitis 1 patient.

with the statement that no hypertonia of the bladder wall occurs after irradiation therapy However, he reports on no control material, the patients in his series were examined 3 months to 6 years after irradiation therapy, and they were not classified in any way It is of interest to note that the mean value curve of Group III, when compared with that of Group II, was found to have shifted to the right i e towards the normal curve In other words, the change in bladder function caused by irradiation therapy is to some extent reversible This accords well with Muth s later studies (1959) in which he found roentgenologically that hydronephrosis provoked by irradiation treatment was partly reversible in character

No severely contracted bladders were found The smallest bladder capacity recorded was 250 ml and the two special cases with bladder capacities of 150 and 175 ml respectively (Fig 2), could be accounted for The results concur with Lindholm s (1960) investigations and with Youssef s (1956) cystometric

observations of bladder lesions The part played by infection in the aetiology of the urological complications of patients with cervical cancer has also been recently emphasized (Muth, 1959, *Hofmann and Kunzler, 1959*) Microscopic examination of all urine sediments in the present series of 68 patients, revealed only one case of urinary tract infection

SUMMARY

The cystometric curves of patients with cancer of the uterine cervix treated by irradiation, and clinically free from relapse are presented in the form of mean value curves for each of the three categories into which the series was divided Group I consisted of those whose treatment had been completed less than 1 year previously Group II those whose treatment had been completed 1–3 years previously, and Group III those who had been treated over 3 years before The curves are compared with those of a similar series plotted prior to therapy It is found that the basic shape of the curves underwent a change indicating that the bladder capacity was reduced and tone increased as a result of therapy These functional changes were most prominent 1 to 3 years therapy When more than 3 years had elapsed from treatment bladder capacity was again found to increase somewhat while its tone approached the normal Irradiation therapy of cancer of the uterine cervix therefore is found to produce changes in bladder function that are to some extent reversible

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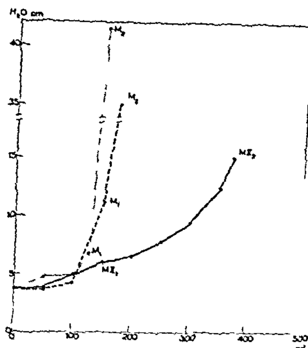


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for their symptoms Eighty two of the women were pregnant. Five of the women had diabetes Thirteen had been treated previously with gentian violet with little or no success

A further number of women were also treated, but the effect of the treatment was not noted in the record sheets or the women did not return, so that the effect of treatment is not known

Only clinically typical cases of vaginal candidiasis were included in the investigation The diagnosis was confirmed by culture from the vaginal content in 61 per cent and by direct microscopy in 39 per cent The type of Candida was usually determined in the cultures from the non pregnant women but not from those who were pregnant

After preliminary trials with vaginal pessaries the preparation was used in gel form in the present investigation [Kindly prepared by the courtesy of AB Pharmacia, Uppsala] Two preparations were used

1) 1 % Cu oxine complex in Mucilan gel prepared by mixing equivalent amounts of oxiquinoline sulphate and copper sulphate The gel was buffered to pH about 9 0 by addition of 1 % borax
2) 1 % isolated Cu oxine-complex substance in Mucilan gel The gel was buffered to pH about 9 0 by addition of 1 % borax

Slight variations in composition were made In in vitro tests the isolated Cu-oxine complex was found to have a somewhat stronger inhibitory effect on Candida than the mixture of copper sulphate and oxine but no difference could be demonstrated clinically Neither was any difference found in the clinical effect of preparations of somewhat different compositions

All cases are therefore presented as a single group

Each patient was given a plastic syringe and a tube of gel sufficient for about one week s treatment The woman was instructed to empty a syringe full of gel into the vagina every morning and every evening If the itching was very troublesome she was instructed to apply the gel also to the vulva for the first few days of treatment

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TREATMENT OF VAGINAL CANDIDIASIS WITH CU-OXINE-COMPLEX

BY

SVEN SJÖSTEDT

In recent years Candida albicans has became increasingly important as a cause of disease in human beings This is due, among other things, to the increasing frequency of diabetes and to the more common use of broad spectrum antibiotics In a search for an antimetabolic capable of inhibiting the life processes of the funges by investigating the demands of fundamentally important *substances as well as the requirement of vitamins and trace elements*, Nordbring-Hertz (1955) discovered that 8 hydroxyquinoline (oxine), which has relatively long been used in agriculture as an inhibitor of Fusarium, Ceratostomella and Penicillium (Zentmeyer, 1943, 44), had a pronounced inhibiting action on the growth of Candida albicans As in the treatment of other microorganisms (Sorkin *et al* 1951), addition of copper potentiated the effect of the oxine on Candida Nordbring-Hertz also showed that the *highly stable* Cu *oxine-complex has an even* stronger effect on Candida Since it was known that other oxiquinoline preparations can be administered by mouth as well as locally to the vagina, it was decided to study the effect of Cu oxine-complex on vaginal candidiasis

Series and Treatment

The series consisted of 112 women with vaginal candidiasis who had sought advice at the Department of Gynæcology in Lund

for their symptoms Eighty two of the women were pregnant. Five of the women had diabetes Thirteen had been treated previously with gentian violet with little or no success

A further number of women were also treated, but the effect of the treatment was not noted in the record sheets or the women did not return, so that the effect of treatment is not known

Only clinically typical cases of vaginal candidiasis were included in the investigation The diagnosis was confirmed by culture from the vaginal content in 61 per cent and by direct microscopy in 39 per cent The type of Candida was usually determined in the cultures from the non pregnant women but not from those who were pregnant

After preliminary trials with vaginal pessaries the preparation was used in gel form in the present investigation (Kindly prepared by the courtesy of AB Pharmacia, Uppsala) Two preparations were used

1) 1 % Cu oxine complex in Mucilan gel prepared by mixing equivalent amounts of oxiquinoline sulphate and copper sulphate The gel was buffered to pH about 9 0 by addition of 1 % borax
2) 1 % isolated Cu oxine-complex substance in Mucilan gel The gel was buffered to pH about 9 0 by addition of 1 % borax

Slight variations in composition were made In *in vitro* tests the isolated Cu oxine complex was found to have a somewhat stronger inhibitory effect on Candida than the mixture of copper sulphate and oxine but no difference could be demonstrated clinically Neither was any difference found in the clinical effect of preparations of somewhat different compositions

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Each patient was given a plastic syringe and a tube of gel sufficient for about one week s treatment The woman was instructed to empty a syringe full of gel into the vagina every morning and every evening If the itching was very troublesome she was instructed to apply the gel also to the vulva for the first few days of treatment

Results

The results are given in Table I.

Table I. *Treatment of Vaginal Candidiasis with Cu-oxine-complex*

		Healed	Improved	No Effect	Recurrence	Could not Tolerate Treatment	Diagnosis: Culture	Diagnosis: Microscopy
Pregnant	Non diabetics	76	3	2	17	2	48	33
	Diabetics	1					1	
Non pregnant	Non diabetics	25		1	3		16	10
	Diabetics	3	1				3	1

It is clear from the Table that treatment produced the desired effect in 105 of 120 women. As a rule, the symptoms disappeared promptly, usually within 1–3 days treatment. Many of the women who had had thrush during earlier pregnancies described the Cu-oxine-complex as more effective than gentian violet. In 4 cases a distinct improvement occurred while in 3 no effect could be demonstrated with certainty. Two of the patients reported that they could not tolerate the treatment because of irritation and sensation of burning in the vulva. Both had very severe vulvovaginitis and both showed objective improvement.

Twenty women had recurrences, sometimes on two or more occasions. In 11 the recurrences responded well to a second course of treatment with Cu-oxine-complex, 3 were afterwards treated alternately during pregnancy with gentian violet painting and Cu-oxine-complex with repeated recurrences, 3 were painted with gentian violet only and with a relatively poor effect, one with oxine and trichamycine with a good effect and in 2 of the cases nothing is known of any further treatment.

Discussion

Oxiquinoline preparations represent the active principle in various therapeutic agents for vaginitis. Some oxiquinoline preparations have been studied for their fungostatic effect on Candida. Rieth

and Schonfeld (1954) found that nitrated oxiquinoline in a concentration of 1 2000 completely inhibited the growth of Candida Brun *et al* (1953), who used the filter paper technique *in vitro*, studied the effect of dichloroxyquinaldine and dichloroxychinoleine They found both substances in a concentration of 0 05-0 1 γ/ml to inhibit the growth of Candida Littman (1955) found 8 hydroxy-7 iod 5 chlorquinoline (Vioform) in a concentration of 4 γ/ml and 5,7 dichlors 8 oxyquinaldine (Sterosan) in a concentration 1 5 γ/ml to have a fungostatic effect. On addition of 10 % serum it was necessary to double the concentration Variation of the pH between 4 5 and 7 4 had no significant effect on the results of treatment

The results described by Nordbring Hertz (1955) were largely the same as those reported by Littman The Cu oxine-complex inhibited growth of *Candida albicans in a concentration* of 5 10⁻⁶M Oxine sulphate by itself produced complete fungostasis in a concentration of 3 10⁻⁵M Studies with the Warburg technique showed that in these concentrations the effect was fungostatic rather than fungocidal Addition of 10 % serum did not markedly reduce the effect of oxine sulphate On the other hand, the effect decreased with decreasing pH Thus the inhibiting action of 10⁻⁶M oxine sulphate at pH 5 5 was abolished at pH 4 5 At a concentration of 10⁻⁵ M the inhibiting action totally disappeared at pH 3 6 At a concentration of 10⁻⁴ M oxine sulphate the action was only slightly decreased by lowering pH and at pH 3 5 there was still about 70 per cent inhibition If Cu oxine-complex was used essentially the same behaviour was observed Owing to greater stability of this complex, an inhibiting effect was still obtained at a pH 3 and 10⁻⁵ M concentration of Cu-oxine complex Nordbring Hertz also compared the effect of oxine sulphate on 40 different Candida strains of which somewhat more than half emanated from patients who were afterwards treated with Cu-oxine-complex No strain was found resistent 3 10⁻⁵ M oxine sulphate

The first clinical studies were carried out by Hesseltine and Beckette (1949) who examined a preparation in which the active substance was believed to be ricinoleic acid It was however afterwards found that the preparation also contained 0 1 %

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Oxiquinoline preparations represent the active principle in various therapeutic agents for vaginitis Some oxiquinoline preparations have been studied for their fungostatic effect on *Candida* Rieth

as the active agent Clinical healing was noted in 94 per cent Recurrences appeared in 18 per cent. Most of these recurrences also responded well to treatment with the gel

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oxyquinoline In 98 cases of vaginal mycosis healing was achieved in 79 per cent The healing rate among the non-pregnant women was 90 per cent Hesseltine (1955) reported later that a preparation containing 3 % ricinol acid and 0 5 % oxyquinoline sulphate is very useful in the treatment of mycotic vulvitis and superior to painting with gentian violet Saucier and Simard (1955) reported on a series of cases of vaginitis – due among other things to Candida – treated with propionic acid and di iodo hydroxyquinoline Treatment was successful in 80 per cent of 40 cases In a similar unspecified series consisting of 134 cases, including Candida vaginitis, cases of vaginitis were successfully treated with dichloroxyquinaldine (Kronig 1958) Rieben (1958) treated 39 cases of vaginal mycosis with the same preparation Treatment produced the desired result in all of the non pregnant women Culture after treatment showed no growth of Candida in 77 per cent of the pregnant women Wenner (1958) and Ruther *et al* (1958) also found dichloroxyquinaldine to be effective in the treatment of vaginal candidiasis

In the present study Cu-oxine-complex produced clinical healing in 94 per cent After treatment no specimens were cultured to show that the fungi had disappeared The value of such culture is doubtful because Candida sometimes occurs in the vagina without producing any symptoms As in other series, the frequency of recurrences was relatively high but most of these recurrences responded well to a second course of treatment A few cases were resistant also to other agents, usually gentian violet

A comparison with other preparations (gentian violet, nystatin, trichamycine) against vaginal candidiasis is difficult, mainly because the criteria for classification of a case as healed varies from one author to another It may nevertheless be claimed that the results obtained with Cu-oxine-complex compare favourable with the best achieved with other agents

SUMMARY

One hundred and twelve patients (82 pregnant) with vaginal canadidiasis were treated with gel containing Cu oxine-complex

examination did not disclose any abnormality In order to exclude the possible presence of genital tuberculosis endometrial biopsy and hystero-salpingography were carried out *Pathological report* Non specific endometritis

Bacteriological examination of the endometrium by guinea pig inoculation was negative

Hystero-salpingography disclosed a uterus bicornis The right tube filled normally and there was immediate peritoneal spill The uterine end of the left tube also filled but was seen to communicate distally with a loculated cavity There was no peritoneal spill on this side

Two years later the patient was re admitted because of the increasing severity of the pain in the left iliac fossa On *gynæcological examination* the slight tenderness over the left adnexa persisted Another *hystero salpingogram* was performed As on the previous occasion it disclosed that the uterine end of the left tube filled in addition the contrast medium now passed from that part into the sigmoid colon (Fig 1) Thus proved the presence of a fistula between the left Fallopian tube and the large intestine However X ray examination of the colon by means of a barium enema did not disclose any abnormality

The patient was again subjected to surgery It was found that the uterine end of the left tube communicated with the sigmoid colon through a small fistula After removal of the stump of the tube and the left ovary and resection of the fistula the opening in the colon was closed The right tube and ovary appeared to be normal *Pathological report* A piece of the wall of the colon with a fibrotic muscular layer A duct like formation which lacks epithelium and is surrounded by a thin layer showing massive lymphatic infiltration extends in the intestinal wall Several endometrial foci with dilated glands lie around the part of the duct which extends into the muscle layer of the intestinal wall The tubal mucosa shows round cell infiltration There are no signs suggestive of tuberculosis

Case 2 The patient had previously been healthy Menstruation was associated with slight pain occurred every 28 days and lasted 5 to 6 days At the age of 21 years she was admitted to hospital because of metrorrhagia *Gynæcological examination* did not

Borell U Fernström I and Rignell S Acta obst. et gynec. Scandinav 40 416 1961

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ENTERO-TUBAL FISTULÆ DIAGNOSED BY HYSTERO-SALPINGOGRAPHY

BY

U BORELL I FERNSTRÖM AND S RIGNELL

According to the literature entero-tubal fistulæ are rare They cause, if anything, non-specific symptoms and are therefore difficult to diagnose pre-operatively, being generally discovered accidentally at an operation for some other cause However, the extensive use of hystero-salpingography during the past ten years has resulted in the disclosure of a steadily increasing number of cases

As we had recently seen 3 cases in which an entero tubal fistula was revealed by hystero-salpingography we thought that a report of the histories of these patients might be of interest

Report of Cases

Case 1 The patient had previously been healthy Menstruation was painless, occurred every 28 days, and lasted 5-6 days At the age of 19 years she had an exploratory laparotomy because of persisting pain in the left iliac fossa The major part of the left Fallopian tube was removed on account of inflammatory changes *Pathological report* Non-specific chronic inflammation

Three years later the patient reported again because of persisting lower abdominal pain identical in character with that which she had experienced prior to the operation *Gynæcological*

examination did not disclose any abnormality In order to exclude the possible presence of genital tuberculosis endometrial biopsy and hystero salpingography were carried out. *Pathological report* Non specific endometritis

Bacteriological examination of the endometrium by guinea-pig inoculation was negative

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Case 2 The patient had previously been healthy *Menstruation was associated with slight pain* occurred every 28 days and lasted 5 to 6 days At the age of 21 years she was admitted to hospital because of metrorrhagia *Gynæcological examination* did not



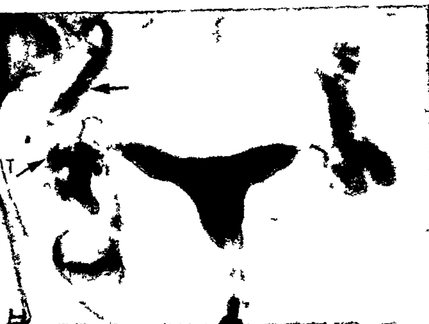
Fig 1 Case 1 Hystero salpingogram showing a fistula between the left Fallopian tube (arrow marked T) and the sigmoid colon (unmarked arrow)

disclose any abnormality Curettage was performed and provided copious curettings *Pathological report* Cervicitis and chronic non specific endometritis

Six months later she was re-admitted because of primary infertility *Hystero salpingography* revealed bilateral hydrosalpinx There was no peritoneal spill but the right tube communicated with the appendix (Fig 2) As tuberculous salpingitis was suspected curettage was carried out *Pathological report* Endometrium in the menstrual phase showing chronic non specific inflammatory changes

Guinea pig inoculation and culture of menstrual blood was negative

Six months later *gynæcological examination* disclosed a hard nodular swelling the size of a tennis ball on the left side The right parametrium was indurated but no swelling was palpated Subjectively, the patient was symptom free On the basis of the gynæcological findings laparotomy was carried out Both tubes



F g 2 *Case* 2 Hystero-salpingogram showing a f stula between the right Fallop an tube (arrow marked T) and the appendix (unmarked arrow)

were one cm thick and firm their abdominal ends were bound down by adhesions The appendix was firmly adherent to the right tube and to the uterine cornu The appendix and the right tube were removed Injection of contrast medium into the opera tion specimen demonstrated a fistula between the tube and the appendix *Pathological report* Chronic salpingitis of non specific character

Case 3 The patient had previously been healthy Menstruation was painless occurred every 28 days and lasted 2 to 3 days At the age of 20 years she had pleurisy At the same age laparotomy was performed because appendicitis was suspected At the ope ration tuberculous peritonitis was diagnosed Four years later she reported again because of undue fatigue X ray examination of the lungs disclosed a small tuberculous focus in the apex of the left lung Eight months later the patient was taken acutely ill with



Fig 3 *Case 3* Hystero salpingogram showing a fistula between the right Fallopian tube (arrow marked T) and the rectum (unmarked arrows)

abdominal pain associated with pyrexia *Gynæcological examination* disclosed a tender swelling, 10 cm in diameter which bulged into the posterior fornix to the right of the body of the uterus At puncture of the swelling through the posterior fornix fluid was obtained Guinea pig inoculation and culture of the fluid confirmed the presence of a tuberculous infection The patient was given a course of streptomycin combined with isoniazid for two months Following this treatment *hystero salpingography* was performed Both tubes were found to be markedly dilated the tubal walls showing irregularly shaped fistulæ (Fig 3) The contrast medium was seen to pass from the distal part of the right tube into the ampulla of the rectum This proved the presence of a fistula *As the patient was symptom free she was not operated* on

Discussion

Entero-tubal fistulæ may form following an operation on the reproductive organs In the majority of cases, however, the underlying cause is infection, commonly an inflammatory process in the adnexal organs and less frequently in the colon Most workers are agreed that the infection usually is of tuberculous origin (Wetterdal 1925, Kinnunen, 1949, Stallworthy, 1952, Rozin, 1954 Gaudefroy, 1958) A tumour appears to give rise to a fistula only in exceptional cases The incidence is difficult to assess, for in many cases co existing infection may be the cause of the fistula (Pelkonen 1935)

Relatively few cases of entero tubal fistulæ have been reported in which the diagnosis was made pre operatively by hystero salpingography or a barium enema into the colon The essential features of the histories in previously published cases and in the 3 cases now presented are summarized in Table I

The Table shows that fistulæ between the left tube and rectum or sigmoid colon were commonest (10 out of 15 cases) In the remaining cases fistulæ between the right tube and the rectum, appendix cæcum and ileum respectively were present In the majority of cases salpingitis was the principal ætiological factor

In Case 1 of the 3 cases presented here the lesion probably arose following inadequate surgery At operation one tube was found to show chronic inflammatory changes and was therefore partially excised Endometriosis developed in the stump of the tube remaining and probably involved the fistula Endometriosis alone or in combination with an infection may have accounted for the fistula in this case

In Case 2 the fistula between the tube and appendix probably arose spontaneously following salpingitis Neither the histological nor the bacteriological examination of the endometrium or the microscopical examination of the removed tube disclosed any signs suggestive of tuberculosis It should be mentioned however that the histological as well as the bacteriological diagnosis of tuberculosis may present considerable difficulty (Rozin 1954)

In Case 3 there was little doubt that the fistula between the tube and rectum was of tuberculous origin

Table I *Essential Features of the Histories in Previously Published Cases and in the Three Cases Presented*

Age of Patient	Type of Fistula	Diagnosis Made At	Ætiology	Authors	
32	Left tube – rectum	Autopsy	Periproctitis (lymphogranuloma venereum)	J O Bower and J C Burns	1945
29	Left tube – sigmoid colon	Barium enema into the colon	Salpingitis (non specific)	E J Croce	1947
31	Left tube – sigmoid colon	Hystero salpingography	Salpingitis (tuberculous?)	M Vesell	1948
22	Left tube – sigmoid colon abdominal wall	Laparotomy + hystero salpingography	Salpingitis (tuberculous)	O Kinnunen	1949
60	Left tube – sigmoid colon	Laparotomy	Diverticulitis	L Woodrow Cox	1952
25?	Right tube – sigmoid colon	hystero salpingography	Salpingitis (tuberculous?)	S Rozin	1954
24	Left tube – sigmoid colon	Hystero salpingography	Salpingitis (tuberculous)	S Rozin	1954
–	Right tube – cæcum	Hystero salpingography	Appendicitis?	S Rozin	1954
–	Right tube – sigmoid colon	Hystero salpingography	Salpingitis (tuberculous?)	S Rozin	1954
69	Left tube – sigmoid colon	Hystero salpingography	Diverticulitis	W R Merz	1956
35	Right tube – appendix	Laparotomy	Appendicitis	W R Merz	1956
32	Right tube – ileum	Hystero salpingography	Salpingitis (tuberculous)	M Gaudefroy and M Potie	1958
24	Left tube – sigmoid colon	Hystero salpingography	Endometriosis?	Borell Fernstrom and Rignell	1961
21	Right tube – appendix	Hystero salpingography	Salpingitis	Borell, Fernstrom, and Rignell	1961
24	Right tube rectum	Hystero salpingography	Salpingitis (tuberculous)	Borell, Fernstrom and Rignell	1961

The presence of a fistula between the tube and intestine is suggested in cases in which an abscess in the true pelvis discharges pus *via* the intestine or in which fæces or flatus are passed *per vaginam* (Merz, 1956) Otherwise, the symptoms are non specific and are due to the pre disposing infection

X ray examination of the colon by means of a barium enema may occasionally disclose genito intestinal fistulæ However, it appears to be more difficult to obtain filling of the lesion with this method of examination than at hystero-salpingography The cases reported in the literature in which hystero-salpingography disclosed an entero-tubal fistula whilst a barium enema into the colon failed to confirm its presence, and the 3 cases here presented support this view

Treatment of a genito-intestinal fistula should be surgical despite the fact that it has been reported that the lesion may occasionally heal spontaneously following conservative treatment (Vesell, (1948) As it is generally of tuberculous origin pre operative anti biotic therapy is recommended

SUMMARY

Three cases of entero-tubal fistula are reported which were diagnosed by hystero salpingography and a summary of similar cases published in the literature is given

The lesion causes non specific symptoms and is rarely recog nized pre operatively unless hystero-salpingography is carried out

As a rule inflammatory processes in the adnexal organs or bowel which quite often are of tuberculous origin, account for the lesion

In one of the cases presented, endometriosis may have been a contributory ætiological factor

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ACTA ALLERGOLOGICA

Redacto es K Baa ee Kolding H. Be g and S o kho m P Bonnev e København G ahlm n L nd P F kn S o kho m, H. Hax ha en København S Hel e om S ock m E. Ja ev Køb nhavn W Ke ppo a He ngfors M hob o O o H Ma m os Lund g rt Me København U S a a H ngfors C. E. Son k, He s ngfors Th Tho a Os o B amou Pa is C. J B to London J Du ha ne Bruxe es F J Fa ons Ba elona Jadassohn Genève J Liska Praha U Se af n F en e U Fab ano Al es R o de Jane ro N Ha p n Pa J Lév nton, Bu nos Ai Ch. Su he and M bourn Ed to Ern t Sa én, S o kholm Egon B u København Subed o es H Colldahl S ockho m N Danbo Oslo Z E k on Lih Hels ngfo s Subsc p on Dan Cr 45 — + po age C 5 —

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ACTA ENDOCRINOLOGICA

Ch ef Ed o Chr an Hambu g Copenhagen Manag ng Ed o K P de en B gaa d Copenh g n Lo al Ed o s Fnn Bee Norway Ch Hambu g Denma k A Jo e Germany G J n Ood The Neth land U Uo la F nland H de Wa ev lle Sw e land H W nb dh Swed n Assoc a e Ed o Rol Luf S ockho m Sub p on Dan Cr 50 —

ACTA OPHTHALMOLOGICA

Redac o es S La on Lund B g Ma g. Os o Hans U k Mol e København Ingo f Schiø z O o Mauno Vanna He ngfors Gunna Bah Upp a a O af B gvad København Ed o Ho g r Ehe s Poul B and trup København. Subscr ption Dan C 60 — + pos age C 5 50

ACTA ORTHOPAEDICA SCANDINAVICA

P k Hag und F nda o

Reda o s I a Alvk O o P G K Bn on Aa hu S en F be g S ockho m Job Ha d O o F E. Ka o H nks F Lang nsk o d Helsingfo s G W b g Lu d Ed or S F be g S kho m Red genda urav t S v Ro en Al m nna ukh Ma mö Sw d p Sub p n D n Cr

ACTA PATHOLOGICA ET MICROBIOLOGICA SCANDINAVICA

R da o s C. G Ah trom Lu d, J Eng b eth Holm København O Ja v Abo K A J un n Københa A. L dau Lund O v R nkon H ngfo s Geo g Waa O o Red genda eu av t Tage K mp Tag n v 4 Københa n Subsc p on D n Cr 60 — + pos age C 7 —

ACTA PHARMACOLOGICA ET TOXICOLOGICA

I n S Ph ma log e S nd a e Ed a

R d Gunn Ah g n Lu d Erns Ba any Up a a S end D gaa d M kke en Køb n ha n Os o Dyb bg Os o E k J cobs n K benha n Ja ob Mo and Os o Ca l G Schm e ow Sto kho m A ma Va a n H ki N ls O of Abdon Go bo g Ib Ho m J n Aa h Bu i k S kho m R d genda cu av Knud O Me København Subsc p on Dan C 50 —

ACTA PSYCHIATRICA ET NEUROLOGICA

R d N s Anton Sto kho m. A. B mo d Amste dam E. Busch Køb nh n E. Es t M u d k g F g København H ma H w g København L v d Ho Am e d n Ma Ka H g ors G b L ngfe d Os o G H M n ad K ohn O o H bert O S kho m H S b g Lu d Ar o Sn man H ngfors H g Tom sson R yk a il An Tok d n O o R d genda cu a t Kn d H. K abbe D T z gad 6 K benh S bsc p on Dan. Cr o — + p ag C 6 —

ACTA TUBERCULOSEA SCANDINAVICA

R d o K d W ng K benh n. E. Larmo a Kul a a (F n and H G Haah H n rt J H mbe k Os o Al W g n S ockho m H k e gaa d København John L odq S o kho m A x T n V da sep (No ge) M. R. Heyn us n d B g Ams d m W B oul h B ho Ho nd S g d S g dsson R yk a k. Ed o N Sjö Sct. N o København V S bsc ption Dan C 7 — + pos g Cr 5 —
